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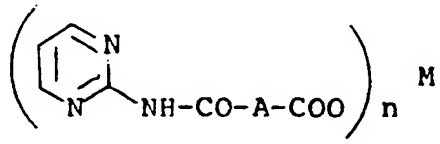
(54) Pyrimidines and their pharmaceutical acceptable salts, and their use as medicines.

(57) 2,6-di-, 2,4,6-, 2,5,6-tri- or 2,4,5,6-tetra-substituted pyrimidines, and 2,6-di-substituted pyridines. These compounds are useful for treatment of neurological deseases.

PYRIMIDINES AND THEIR PHARMACEUTICAL ACCEPTABLE SALTS AND THEIR USE AS MEDICINES

This invention relates to novel pyrimidines or their pharmaceutically acceptable salts, and novel therapeutic agents for neurological diseases of the peripheral and central nervous systems of animals containing the above compounds as active ingredients.

Japanese Patent Publication No. 23,394/1971 discloses that aminopyrimidines represented by the following formula



wherein A represents an alkylene group having up to 16 carbon atoms, or a lower alkylene group substituted by an amino group or a C_{2-5} acylamino group, M represents H, Na, K, NH_4, Mg, Ca or an organic basic ammonium salt, and n is a value equal to the atomic valency of M,
have interesting therapeutic activity, particularly as an anti-melanchoric agent and psychoanaleptic agent in the field of psychosis.

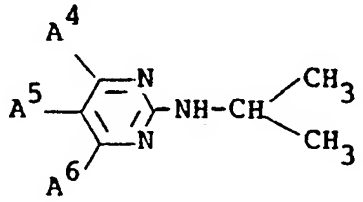
Japanese Patent Publication No. 22044/1976 discloses that dichloro-lower aliphatic carboxylic acid salts of 2-isopropylaminopyrimidine, such as 2-isopropylaminopyrimidine dichloroacetate, are useful as a therapeutic agent for a neurological disease.

Japanese Laid-Open Patent Publication No. 100477/1977 (Patent Publication No. 28548/1984) discloses that 2-isopropylaminopyrimidine phosphate is useful as a therapeutic agent for a neurological disease.

Japanese Patent Publication No. 157575/1979 discloses a process for producing 2-chloropyrimidine in a high yield. A working example in this patent publication describes the preparation of 2-chloropyrimidine in a yield of 69 %.

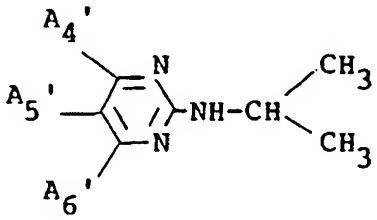
Japanese Laid-Open Patent Publication No. 393/1980 discloses a process for producing 2-isopropylaminopyrimidine in a high yield. A working example of this patent publication describes the preparation of 2-isopropylaminopyrimidine in a yield of 60 %.

Japanese Laid-Open Patent Publication No. 122768/1980 discloses that a hydroxy derivative of 2-isopropylaminopyrimidine represented by the following formula



wherein A^4, A^5 and A^6 each represent H or OH, and at least one of them represents OH,
is useful in the field of nerve regeneration and for treatment of myodystrophy.

Japanese Laid-Open Patent Publication No. 145670/1980 discloses that 2-isopropylaminohalogenopyrimidines represented by the following formula



wherein A_4', A_5' and A_6' each represent H or a halogen atom, and at least one of them is a halogen atom,

are useful for treatment of various neurological diseases and myodystrophy.

Japanese Laid-Open Patent Publication No. 145,671/1980 discloses a process for producing a hydroxy derivative of 2-isopropylaminopyrimidine.

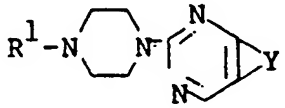
Japanese Laid-Open Patent Publication No. 151,571/1980 discloses that 2-isopropylamino-5-halogenopyrimidines are interesting in the treatment of neurological diseases.

Japanese Laid-Open Patent Publication No. 10177/1981 discloses a process for producing 2-isopropylaminopyrimidine substantially in a quantitative yield by aminolyzing 2-methylsulfonylpyrimidine with isopropylamine.

Japanese Laid-Open Patent Publication No. 26880/1981 discloses a process for producing 2-isopropylaminopyrimidine which comprises reacting bis(isopropylguanidine) sulfate with 1,1,3,3-tetraethoxypropane.

Japanese Laid-Open Patent Publication No. 90,013/1981 describes a therapeutic agent for myodystropy, myopathy, muscle rigidity and/or dysfunction of neuro-musclar transmission comprising substituted derivative of pyrimidine or its therapeutically acceptable salt or its metabolite as an active ingredient. However, it merely discloses various salts such as an orthophosphate, of 2-isopropylaminopyrimidine as an active compound.

Japanese Laid-Open Patent Publication No. 65873/1986 discloses that 2-piperazinopyrimidines of the following formula



wherein R^1 is H or aralkyl, and Y is a divalent organic group defined in the claim of this patent publication, are useful as a herbicide for paddies and upland farms.

The present inventors previously provided a novel therapeutic agent for treatment of neurological diseases comprising a specific 2-piperazinopyrimidine derivative or its pharmaceutically acceptable salt (International Laid-Open No. WO87/04928).

It is an object of this invention to provide novel pyrimidines and their pharmaceutically acceptable salts.

Another object of this invention is to provide therapeutic agents for neurological diseases and spinal breakdown comprising the above novel compounds.

Another object of this invention is to provide a novel therapeutic agent for neurological diseases having the effect of regenerating and repairing nerve cells.

Another object of this invention is to provide a novel therapeutic agent for neurological diseases which can be applied to disorders of peripheral nerves, cerebrospinal injury, etc.

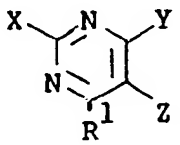
Another object of this invention is to provide a novel therapeutic agent for neurological diseases which can be applied to diseases of central nerves which are different from psycosis and in which abnormality in the operating system or the metabolic system of chemical transmitters is regarded as being primarily involved.

Another object of this invention is to provide a novel therapeutic agent for cerebral diseases which has the effect of improving and restoring learning and memory.

Another object of this invention is to provide a novel therapeutic agent for neurological diseases or cerebral diseases, which comprises a comprehensively excellent and useful compound having pharmacological actions suitable for treatment of neurological diseases or cerebral diseases with little side effects such as liver trouble.

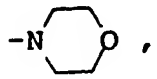
Further objects of this invention along with its advantages will become apparent from the following description.

According to this invention, there is first provided a pyrimidine represented by the following formula (1), or its pharmaceutically acceptable salt

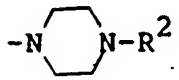


(1)

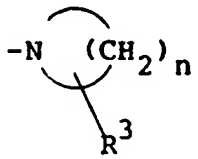
wherein R^1 represents a hydrogen atom or a lower alkyl group; X represents a group of the formula



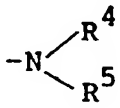
a group of the formula



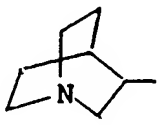
in which R^2 represents a hydrogen atom, a lower alkyl group, a phenyl group, a benzyl group or an alpha-(p-chlorophenyl)benzyl group,
a group of the formula



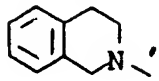
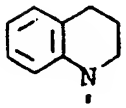
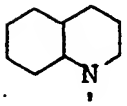
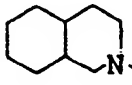
in which R^3 corresponds to one or at least two identical or different substituents replacing one or at least two hydrogen atoms of identical or different methylene groups, and represents a lower alkyl group, a hydroxyl group, a phenyl group optionally substituted by nitro, a benzyl group, a benzoyloxy group, a benzoylamino group, a lower alkylamino group, a di-lower alkylamino group, the $HO(C_6H_5)_2C$- group, a piperidino group, a hydroxy(lower alkyl) group, the $C_6H_5SO_2O$- group, a benzoyl group optionally substituted by halogen, a lower alkylsulfonylamide group or a lower alkoxycarbonyl group, and n is a number of 4, 5, 6 or 7,
a group of the formula



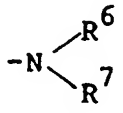
in which R^4 represents a hydrogen atom, a lower alkyl group or a benzyl group, and R^5 represents a lower alkyl group, a lower acyl group, a 2-furoyl group, a benzyl group, a 4-piperidyl group optionally substituted by benzoyl, a phenethyl group, the group



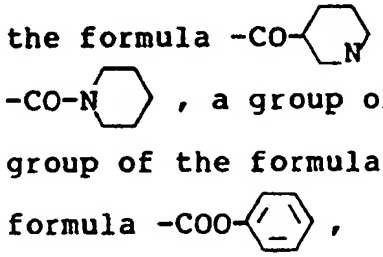
or a benzoyl group optionally substituted by halogen or nitro,

a group of the formula  , a group of the formula  , a group of the formula  , or a group of the formula  ;

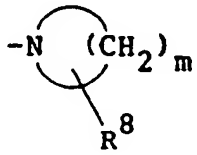
Y represents a group of the formula $-CH_2R^9$
wherein R^9 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, or a di-lower alkylamino group,
a group of the formula



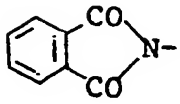
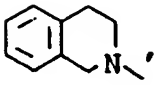
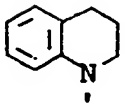
wherein R^6 represents a hydrogen atom, a lower alkyl group, a phenyl group, a benzyl group, a lower alkoxy group or a 2-(N,N-dimethylamino)ethyl group, and R^7 represents a lower alkyl group, a lower acyl group, a cyclohexylcarbonyl group, a 2-furoyl group, a lower alkoxycarbonyl group, a cinnamoyl group, a benzyl group, a benzylcarbonyl group, a tosyl group, a phenoxyacetyl group, a di-lower alkylcarbamoyl group, a 2-thienyl group,

a group of the formula  ,

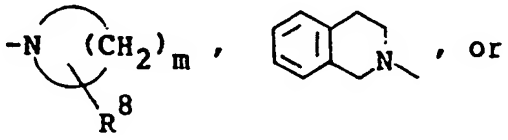
a 4-lower alkylpiperazyl group, or a benzoyl group optionally substituted by halogen, nitro, lower alkyl, lower alkoxy, amino, benzoylamino or phenyl, provided that when R^6 is a hydrogen atom, R^7 is a benzoyl group,
a group of the formula

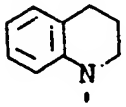
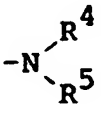


wherein R^8 corresponds to a substituent replacing the hydrogen atom of the methylene group, and represents a hydrogen atom, a lower alkyl group, a phenyl group or a benzyl group, and m is a number of 4, 5, 6 or 7,

a group of the formula  , a group of the formula  , or a group of the formula  ;

and Z represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxycarbonyl group; provided that Y represents $-CH_2R^9$ only when Z is a lower alkoxycarbonyl group; that R^4 represents a hydrogen atom only when R^5 represents a lower alkyl group, a lower acyl group, a 2-furoyl group, a benzyl group, a phenethyl group or a benzoyl group optionally substituted by halogen or nitro, Y represents CH_2R^9 and Z represents a lower alkoxy carbonyl group; that Y can be

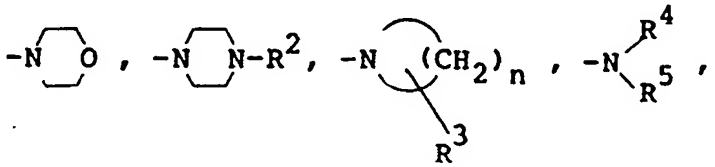


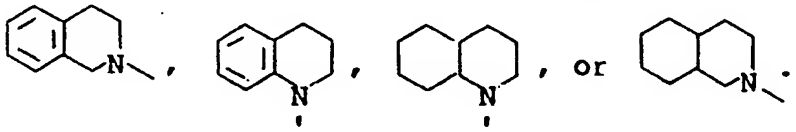
 only when X is 

and R^4 is a lower alkyl group.

In formula (1), R^1 is a hydrogen atom or a lower alkyl group. The lower alkyl group may be linear or branched, and preferably has 1 to 4 carbon atoms. Examples include methyl, ethyl, n-propyl, isopropyl n-butyl, sec-butyl, isobutyl and t-butyl groups.

In formula (I), X represents a group of the formula

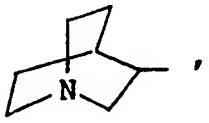




In the above formulae, R^2 represents a hydrogen atom, a lower alkyl group, phenyl group, benzyl group or an alpha-(p-chlorophenyl)benzyl group. Examples of the lower alkyl group may be the same as those exemplified for R^1.

R^3 corresponds to a substituent replacing the hydrogen atom of the methylene group, and represents a lower alkyl group, a hydroxyl group, a phenyl group optionally substituted by nitro, a benzyl group, a benzoyloxy group, a benzoylamino group, a lower alkylamino group, a di-lower alkylamino group, the HO-$(C_6H_5)_2C$-group, a piperidino group, a hydroxy(lower alkyl) group, the $C_6H_5SO_2O$- group, a benzoyl group optionally substituted by halogen, a lower alkylsulfonylamide group, or a lower alkoxycarbonyl group. n is a number of 4, 5, 6 or 7. Examples of the lower alkyl groups may be the same as those exemplified above with regard to R^1.

R^4 represents a hydrogen atom, a lower alkyl group or a benzyl group, and R^5 represents a lower alkyl group, a lower acyl group, a 2-furoyl group, a benzyl group, a 4-piperidyl group optionally substituted by benzoyl, a phenethyl group or the group



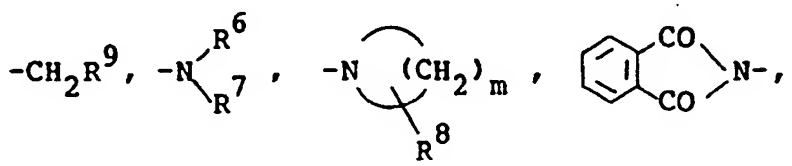
or a benzoyl group optionally substituted by halogen or nitro.

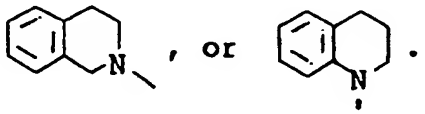
Examples of the lower alkyl groups for R^4 and R^5 may be the same as those R^5.

The alkyl moiety of the lower acyl group for R^5 may be linear or branched.

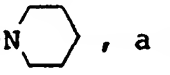
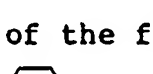
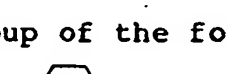
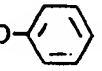
Acyl groups having 2 to 6 carbon atoms are preferred, and examples include acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl and hexanoyl groups.

In formula (I), Y represents a group of the formula





R^9 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, or a di-lower alkylamino group. R^6 represents a hydrogen atom, a lower alkyl group, a phenyl group, a benzyl group, a lower alkoxy group or a 2-(N,N-dimethylamino)ethyl group. R^7 represents a lower alkyl group, a lower acyl group, a cyclohexylcarbonyl group, a 2-furoyl group, a lower alkoxycarbonyl group, a cinnamoyl group, a benzyl group, a benzylcarbonyl group, a tosyl group, a phenoxyacetyl group, a di-lower alkylcarbamoyl group, a 2-thienyl group,

a group of the formula  , a group of the formula  , a group of the formula  , a group of the formula  , a group of the formula  ,

a 4-lower alkylpiperazyl group, or a benzoyl group which may be substituted by halogen, lower alkoxy, nitro, amino, benzoylamino or phenyl.

Examples of the lower alkyl groups for R^9, R^6 and R^7 may be the same as those exemplified with respect to R^1.

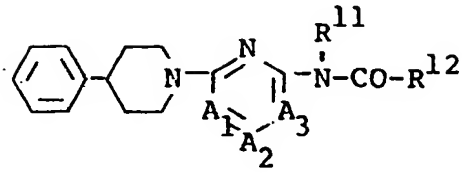
Examples of the lower acyl group for R^7 may be the same as those exemplified above for R^5.

Examples of the halogen and lower alkoxy group as substituent for the benzoyl group R^7 are fluorine, chlorine, bromine and iodine, and alkoxy groups having 1 to 4 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy and sec-butoxy. When R^6 is a hydrogen atom, R^7 is a benzoyl group.

Furthermore, in formula (1), Z represents a hydrogen atom, a halogen atom, a lower alkoxycarbonyl group or a lower alkyl group.

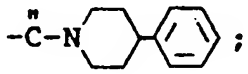
Examples of the halogen atom are fluorine, chlorine, bromine and iodine. Examples of the lower alkyl group may be the same as those exemplified with respect to R^1.

According to this invention, there is further provided a compound represented by the following formula (2), or its pharmaceutically acceptable salt,

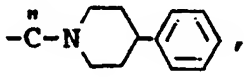


(2)

wherein A_1 represents =CH- or -N=; A_2 is =CH-, -N=, or



A_3 represents =CH- or -N=; R^{11} represents a lower alkyl group; R^{12} represents a phenyl group optionally substituted by halogen, lower alkyl or lower alkoxy, a 2-furyl group, or a 2-thienyl group; provided that when A_1 is -N=, A_2 is

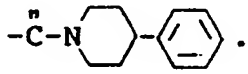


when A_1 and A_2 are =CH-, A_3 is =CH-, and
when A_2 is -N=, A_1 and A_3 are =CH-.

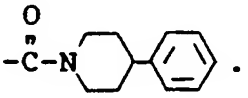
In formula (2), R^{11} is a lower alkyl group. R^{12} represents a phenyl group optionally substituted by halogen, lower alkyl or lower alkoxy, a 2-furyl group or a 2-thienyl group.

Examples of the lower alkyl groups for R^{11} and R^{12} may be the same as those exemplified above with regard to R^1.

A_1 is =CH- or =N-, and A_2 is =CH-, -N=, or



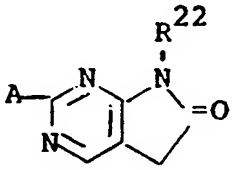
A_3 is =CH- or -N=. When A_1 is -N=, A_2 is



When A_1 and A_2 are =CH-, A_3 is =CH-. When A_2 is -N=, A_1 and A_2 are =CH-.

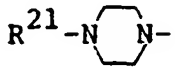
According to still another aspect, there is also provided a novel compound of the following formula (3) having the same pharmacological efficacy.

A pyrimidine of formula (3), or its pharmaceutically acceptable salt,

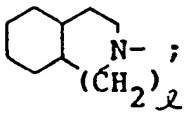


(3)

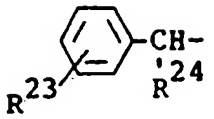
wherein A represents a group of the formula



or a group of the formula

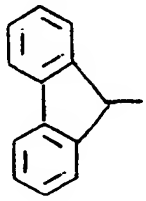


R^{21} represents a group of the formula (a)



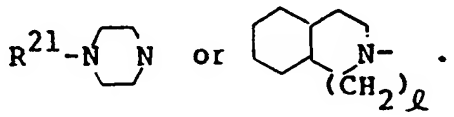
(a)

wherein R^{23} represents a hydrogen atom, a lower alkyl group, a lower alkoxy group or a phenyl group and R^{24} represents a hydrogen atom, a lower alkyl group, a cyclohexyl group, a phenyl group, a 4-halogenophenyl group, a p-diphenyl group, a 2-pyridyl group or a 2-thiophenyl group, provided that R^{23} and R^{24} are not hydrogen atoms at the same time;
or a group of the formula (b)

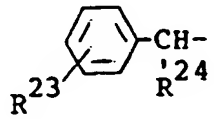


which is a 9-fluorenyl group or a triphenylmethyl group; R^{22} represents a lower alkyl group; and ℓ is a number of 0 or 1.

In formula (3), A represents a group of the formula

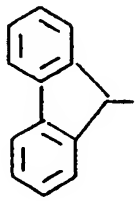


R^{21} represents a group of the following formula (a)



(a)

or a group of the following formula (b)



which is a 9-fluorenyl or triphenylmethyl group.

R^{23} in formula (a) is a hydrogen atom, a lower alkyl group, a lower alkoxy group or a phenyl group, and R^{24} represents a hydrogen atom, a lower alkyl group, a cyclohexyl group, a phenyl group, a 4-halogenophenyl group, a p-diphenyl group, a 2-pyridyl group, or a 2-thiophenyl group. R^{23} and R^{24} and are not hydrogen atoms at the same time.

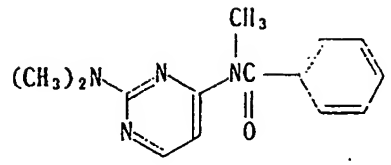
The lower alkyl groups for R^{23} and R^{24}, independently from each other, may be linear or branched and preferably contain 1 to 4 carbon atoms. Examples are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl and isobutyl groups.

The lower alkoxy group for R^{23} may be linear or branched, and those having 1 to 4 carbon atoms are preferred. Examples include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy and t-butoxy groups. Examples of the 4-halogenophenyl group for R^{24} are 4-fluorophenyl, 4-chlorophenyl or 4-bromophenyl.

In formula (3), R^{22} is a lower alkyl group examples of which may be same as those given for R^{23}. t is a number of 0 or 1.

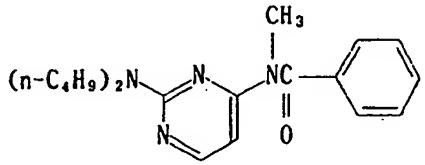
Examples of formulae (1), (2) and (3) provided by this invention are given below.

(100)



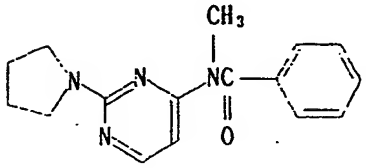
(104) p-Toluenesulfonate of (100)

(108)



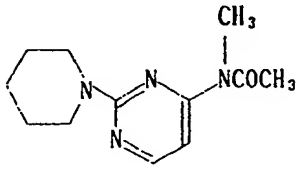
(112) p-Toluenesulfonate of (108)

(116)



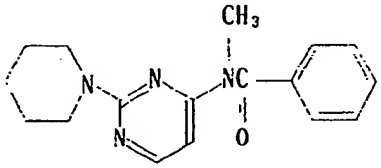
(120) p-Toluenesulfonate of (116)

(124)



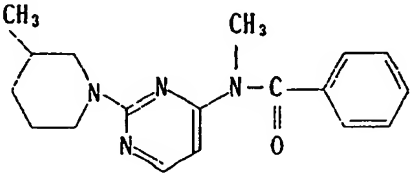
(128) p-Toluenesulfonate of (124)

(132)



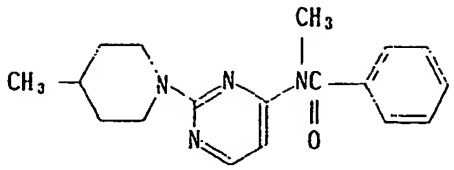
(136) p-Toluenesulfonate of (132)

(137)



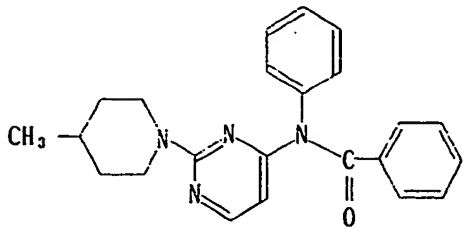
(138) p-Toluenesulfonate of (137)

(140)



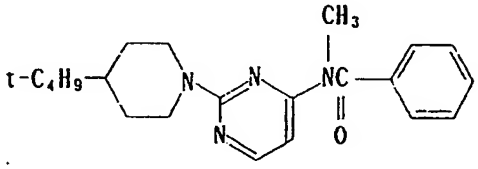
(144) p-Toluenesulfonate of (140)

(149)



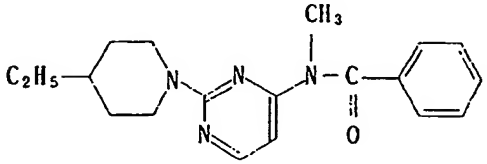
(150) p-Toluenesulfonate of (149)

(148)



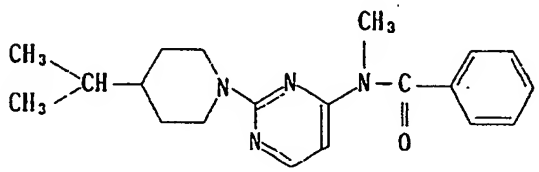
(152) p-Toluenesulfonate of (148)

(145)



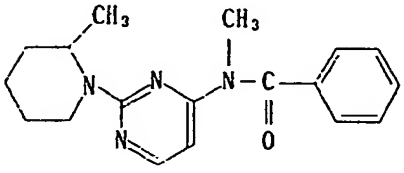
(146) p-Toluenesulfonate of (145)

(147)



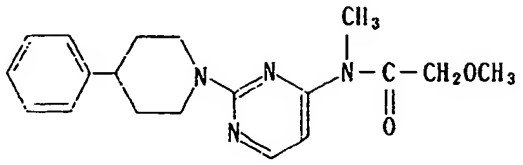
(147-1) p-Toluenesulfonate of (147)

(153)



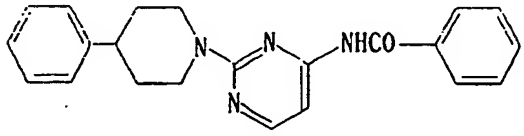
(154) p-Toluenesulfonate of (153)

(154-1)



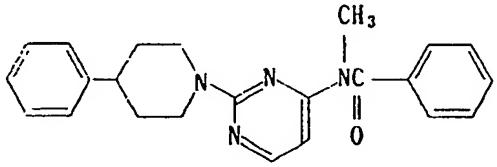
(154-2) p-Toluenesulfonate of (154-1)

(156)



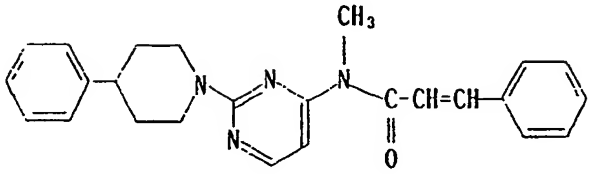
(160) p-Toluenesulfonate of (156)

(164)



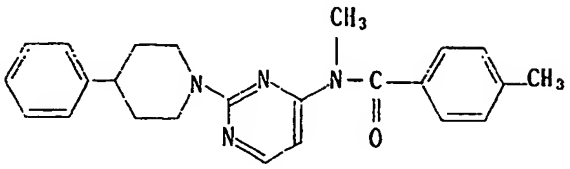
(165) Sulfate of (164)
(166) Phosphate of (164)
(167) Maleate of (164)
(169) Naphthalenesulfonate of (164)
(171) Citrate of (164)
(171-1) Tartarate of (164)
(171-1-1) Fumarate of (164)
(168) p-Toluenesulfonate of (164)
(170) Hydrochloride of (164)

(170-1)



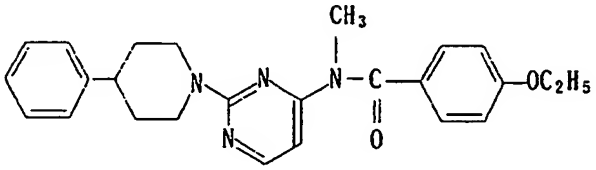
(170-2) p-Toluenesulfonate of (170-1)

(171-2)



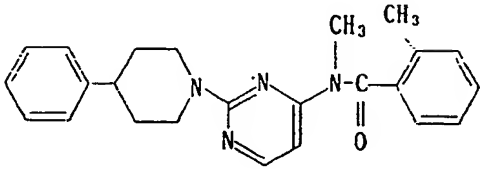
(171-3) p-Toluenesulfonate of (171-2)

(171-4)



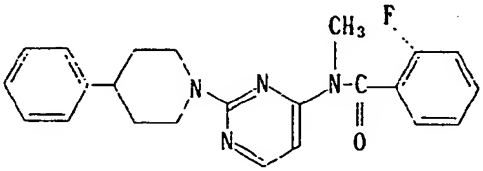
(171-5) p-Toluenesulfonate of (171-4)

(171-6)



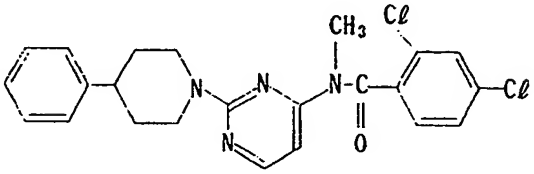
(171-7) p-Toluenesulfonate of (171-6)

(171-8)



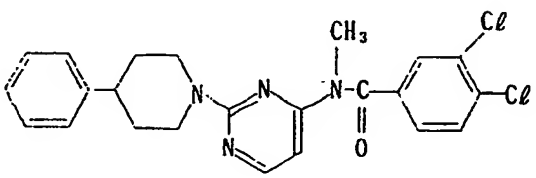
(171-9) p-Toluenesulfonate of (171-8)

(171-10)



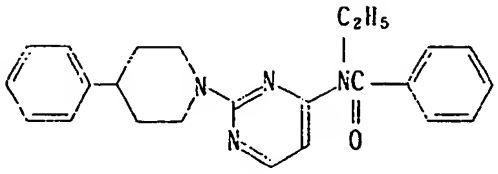
(171-11) p-Toluenesulfonate of (171-10)

(171-12)



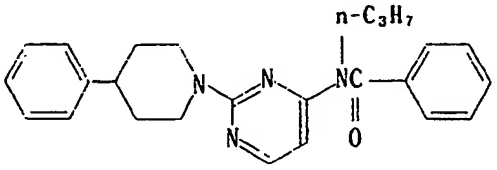
(171-13) p-Toluenesulfonate of (171-12)

(172)



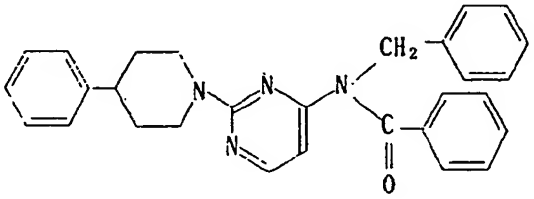
(176) p-Toluenesulfonate of (172)

(180)



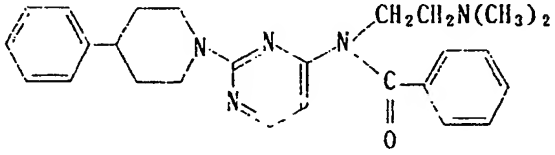
(184) p-Toluenesulfonate of (180)

(188)



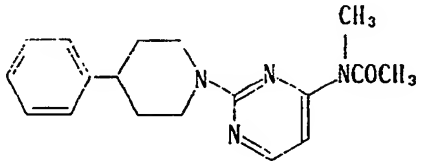
(192) p-Toluenesulfonate of (188)

(196)



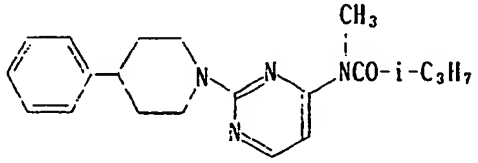
(200) p-Toluenesulfonate of (196)

(204)



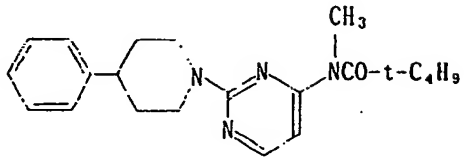
(208) p-Toluenesulfonate of (204)

(212)



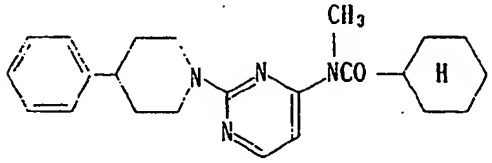
(216) p-Toluenesulfonate of (212)

(220)



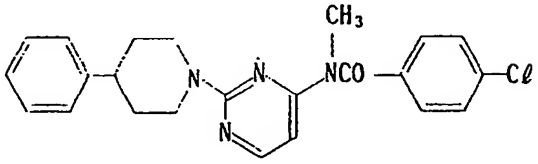
(224) p-Toluenesulfonate of (220)

(228)



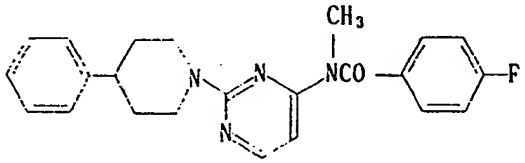
(232) p-Toluenesulfonate of (228)

(236)



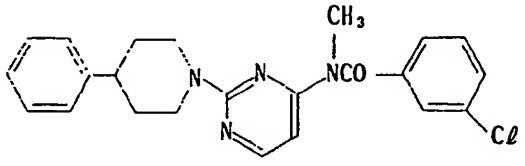
(240) p-Toluenesulfonate of (236)

(241)



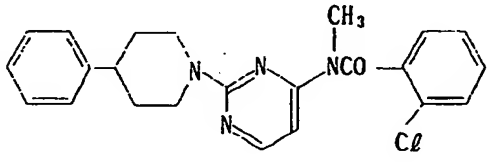
(242) p-Toluenesulfonate of (241)

(244)



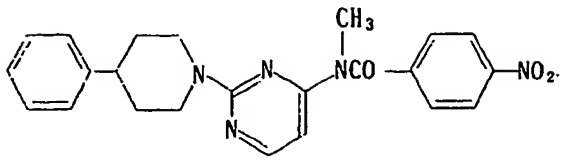
(248) p-Toluenesulfonate of (244)

(252)



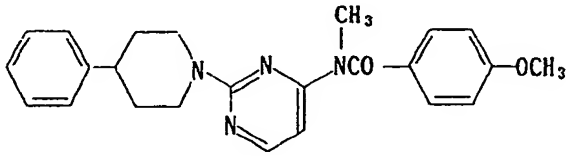
(256) p-Toluenesulfonate of (252)

(260)



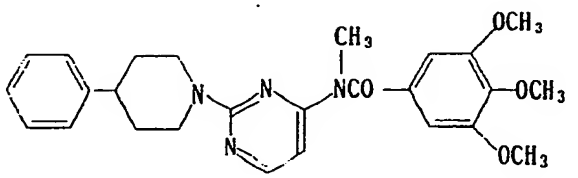
(264) p-Toluenesulfonate of (260)

(268)



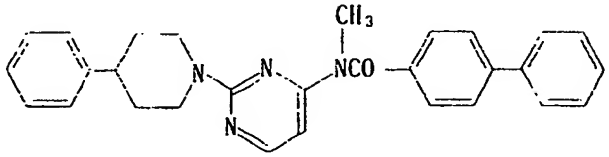
(272) p-Toluenesulfonate of (268)

(276)



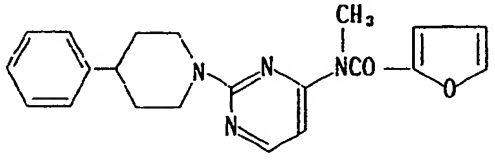
(280) p-Toluenesulfonate of (276)

(284)



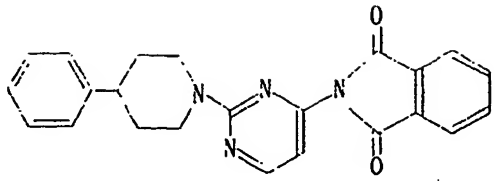
(288) p-Toluenesulfonate of (284)

(292)



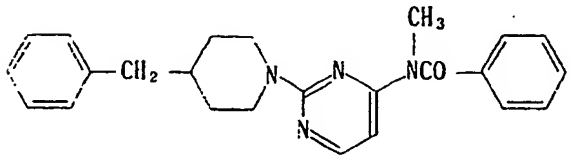
(296) p-Toluenesulfonate of (292)

(297)



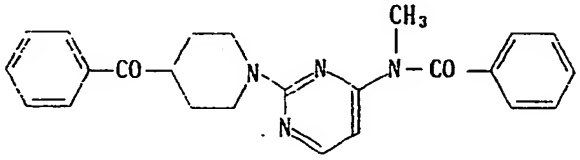
(298) p-Toluenesulfonate of (297)

(300)



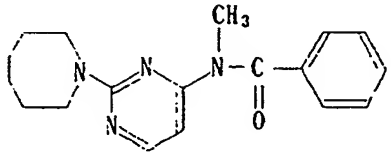
(304) p-Toluenesulfonate of (300)

(305)



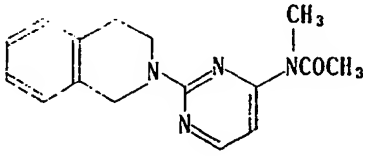
(306) p-Toluenesulfonate of (305)

(307)



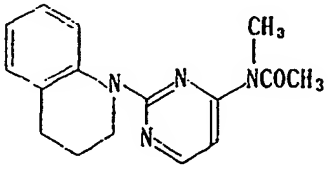
(307-1) Hydrochloride of (307)

(308)



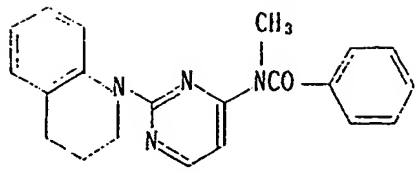
(312) p-Toluenesulfonate of (308)

(316)



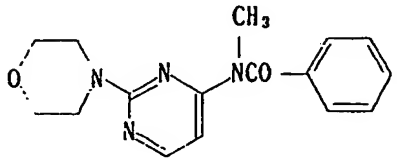
(320) p-Toluenesulfonate of (316)

(324)



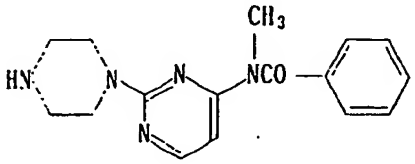
(328) p-Toluenesulfonate of (324)

(332)



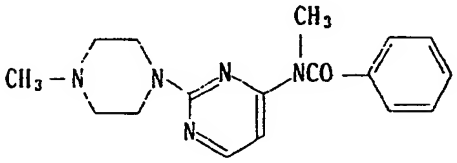
(336) p-Toluenesulfonate of (332)

(340)



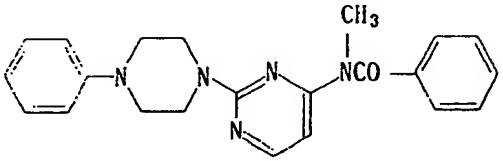
(344) p-Toluenesulfonate of (340)

(348)



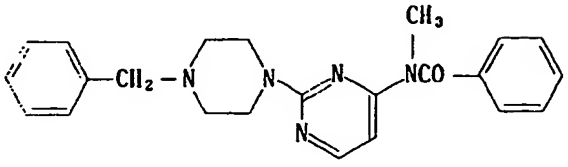
(352) p-Toluenesulfonate of (348)

(356)



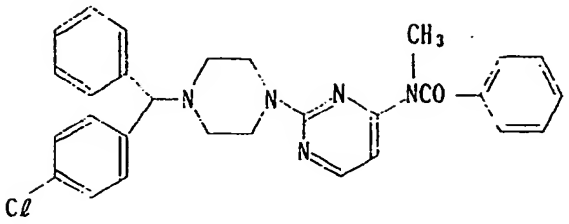
(360) p-Toluenesulfonate of (356)

(364)



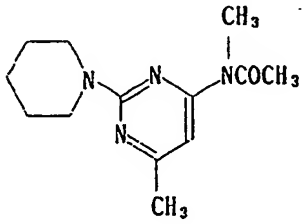
(368) p-Toluenesulfonate of (364)

(372)



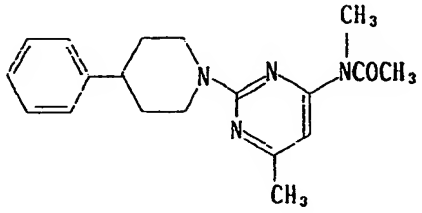
(376) p-Toluenesulfonate of (372)

(380)



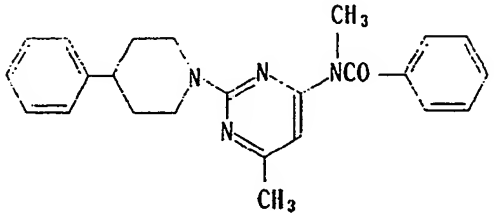
(384) p-Toluenesulfonate of (380)

(388)



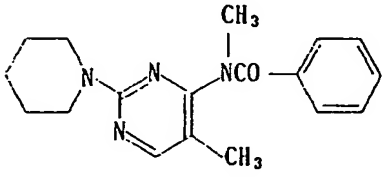
(392) p-Toluenesulfonate of (388)

(396)



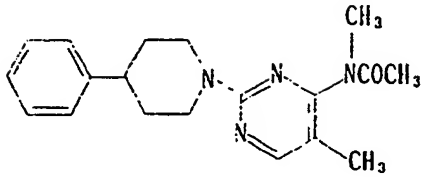
(400) p-Toluenesulfonate of (396)

(404)



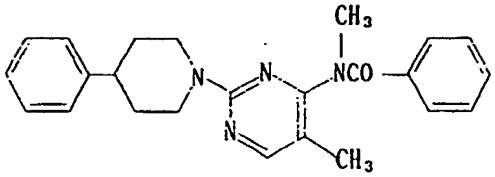
(408) p-Toluenesulfonate of (404)

(412)



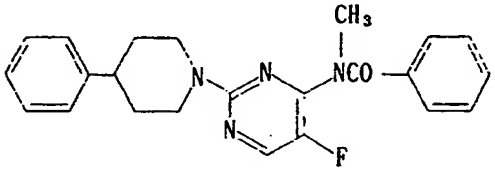
(416) p-Toluenesulfonate of (412)

(420)



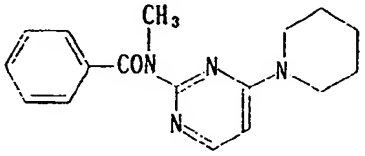
(424) p-Toluenesulfonate of (420)

(428)



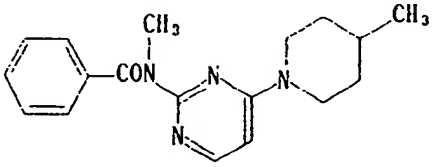
(432) p-Toluenesulfonate of (428)

(600)



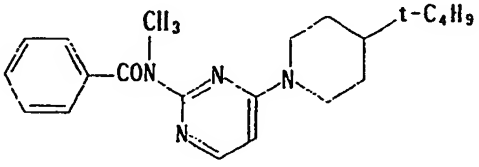
(604) p-Toluenesulfonate of (600)

(608)



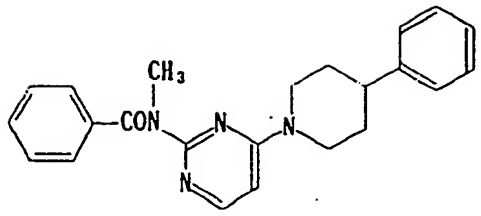
(612) p-Toluenesulfonate of (608)

(616)



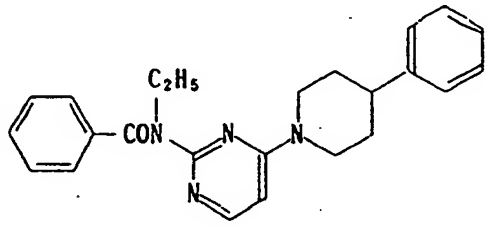
(620) p-Toluenesulfonate of (616)

(624)



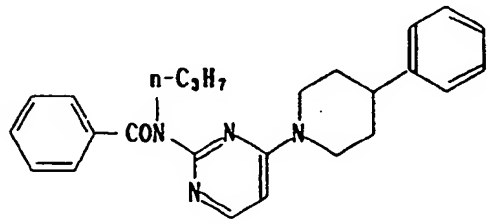
(628) p-Toluenesulfonate of (624)

(632)



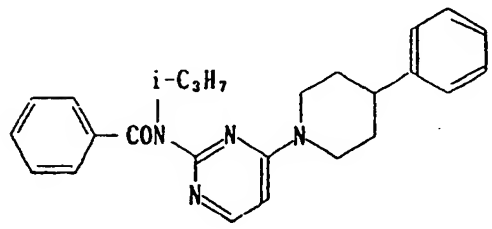
(636) p-Toluenesulfonate of (632)

(640)



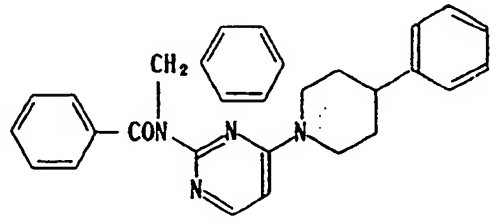
(644) p-Toluenesulfonate of (640)

(648)



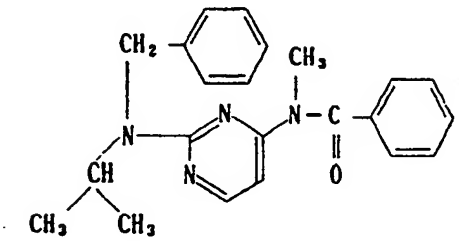
(652) p-Toluenesulfonate of (648)

(656)



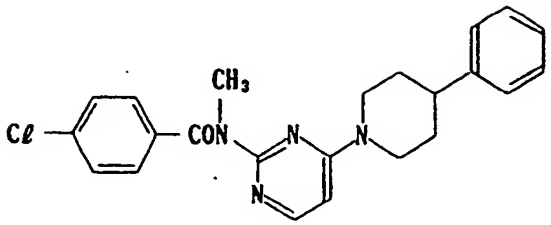
(660) p-Toluenesulfonate of (656)

(661)



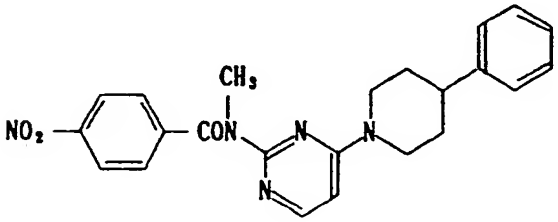
(662) Hydrochloride of (661)

(664)



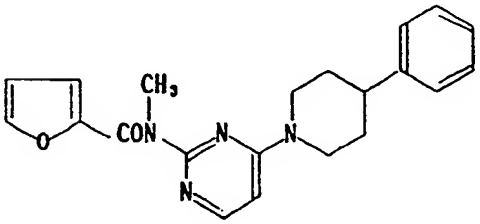
(668) p-Toluenesulfonate of (664)

(672)



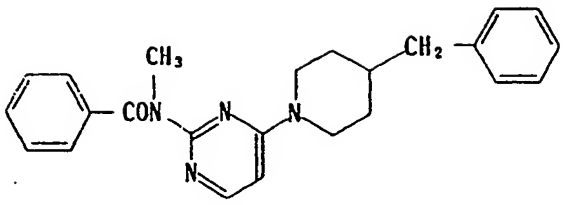
(676) p-Toluenesulfonate of (672)

(680)



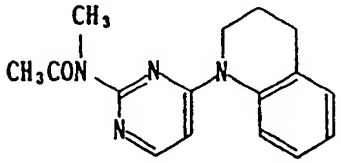
(684) p-Toluenesulfonate of (680)

(688)



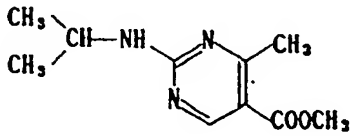
(692) p-Toluenesulfonate of (688)

(696)



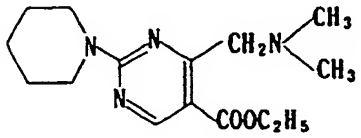
(700) p-Toluenesulfonate of (696)

(800)



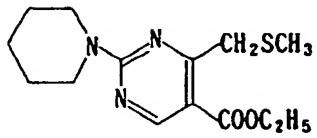
(804) Maleate of (800)

(808)

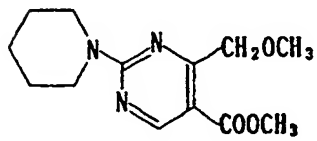


(812) Maleate of (808)

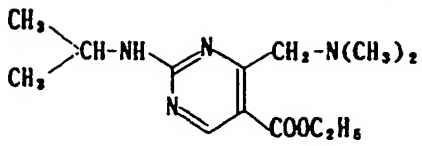
(816)



(820)

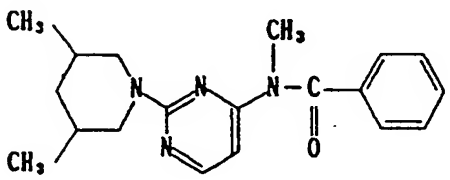


(824)



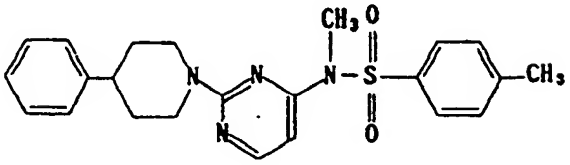
(828) Maleate of (824)

(2000)



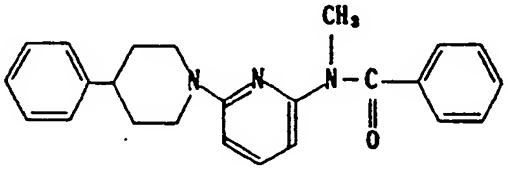
(2004) p-Toluenesulfonate of (2000)

(2008)



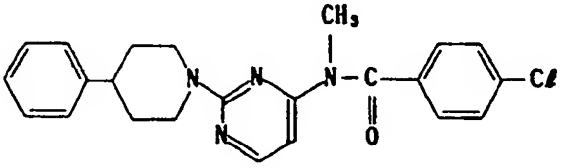
(2012) p-Toluenesulfonate of (2008)

(2016)



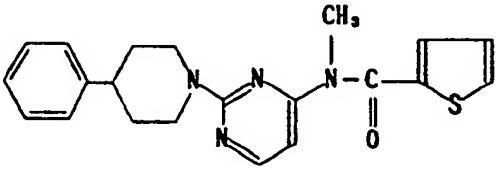
(2020) p-Toluenesulfonate of (2016)

(2022)



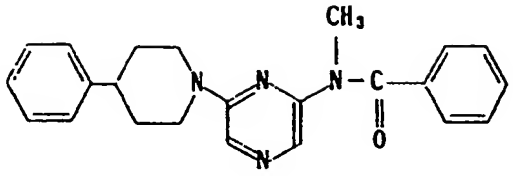
(2022-1) p-Toluenesulfonate of (2022)

(2023)



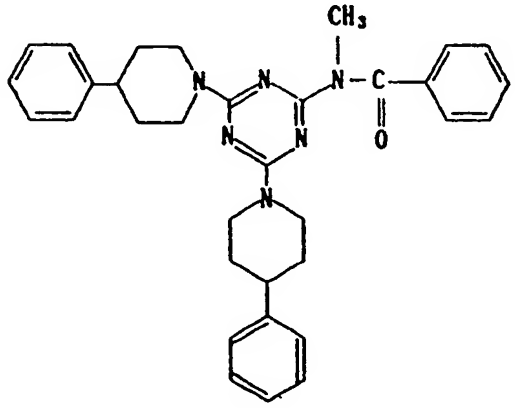
(2023-1) p-Toluenesulfonate of (2023)

(2024)



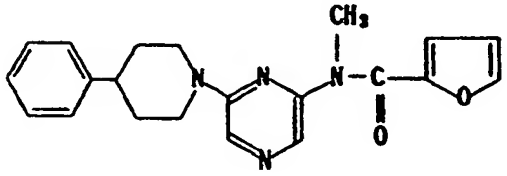
(2028) p-Toluenesulfonate of (2024)

(2032)



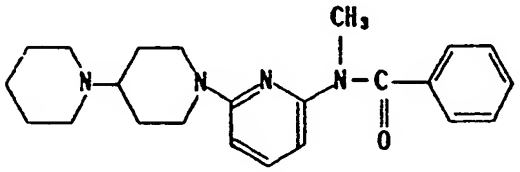
(2036) Di-p-toluenesulfonate of (2032)

(2040)



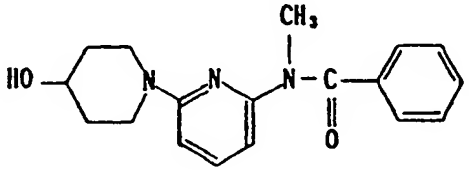
(2044) p-Toluenesulfonate of (2040)

(2048)



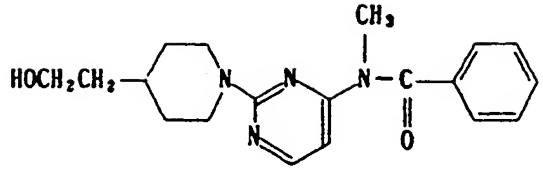
(2052) Dihydrochloride of (2048)

(2056)



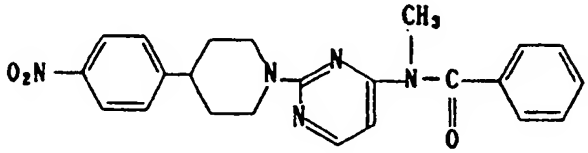
(2060) Hydrochloride of (2056)

(2064)



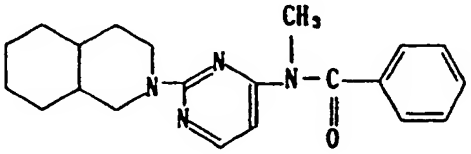
(2070) Hydrochloride of (2064)

(2074)



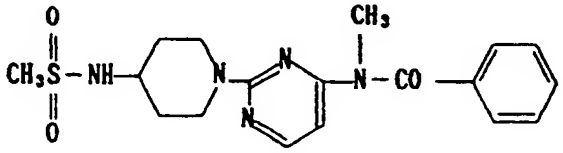
(2076) Hydrochloride of (2074)

(2080)



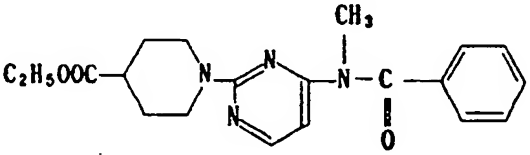
(2084) Hydrochloride of (2080)

(2088)



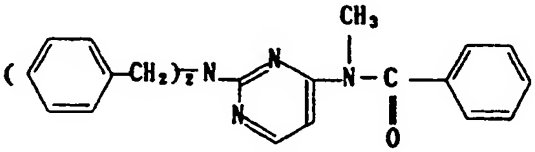
(2092) Hydrochloride of (2088)

(2096)



(2100) Hydrochloride of (2096)

(2104)

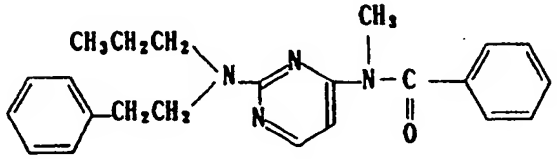


(2108) Hydrochloride of (2104)

(2112)

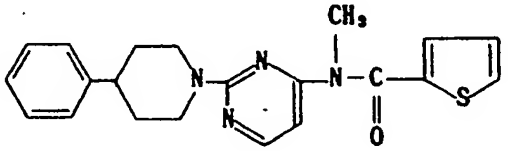
(2116) p-Toluenesulfonate of (2112)

(2120)



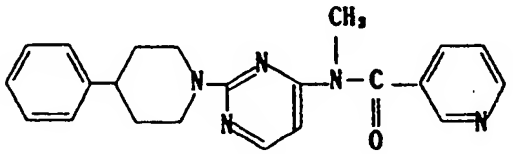
(2124) p-Toluenesulfonate of (2120)

(2128)



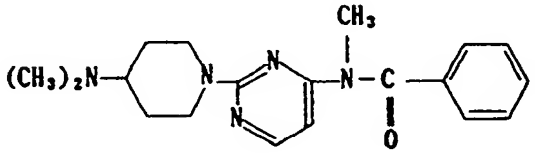
(2132) p-Toluenesulfonate of (2128)

(2136)



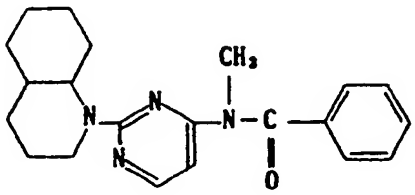
(2140) Di-p-toluenesulfonate of (2136)

(2144)



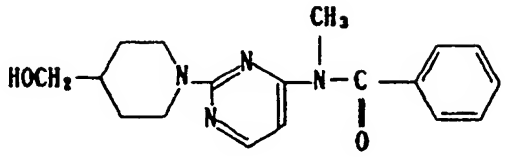
(2148) Dihydrochloride of (2144)

(2152)



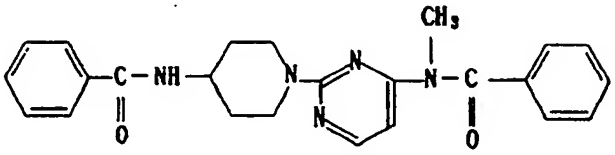
(2156) Hydrochloride of (2152)

(2160)



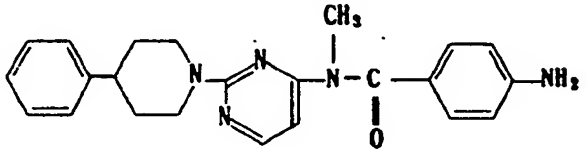
(2164) Dihydrochloride of (2160)

(2170)



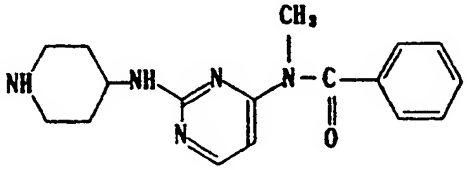
(2174) p-Toluenesulfonate of (2170)

(2178)



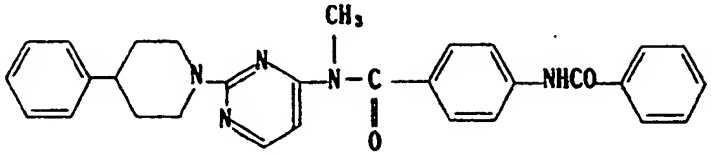
(2182) p-Toluenesulfonate of (2178)

(2184)



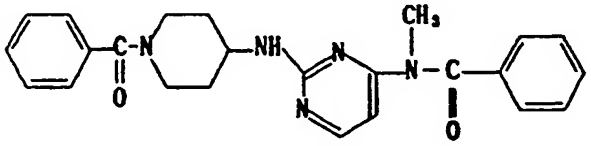
(2188) p-Toluenesulfonate of (2184)

(2192)



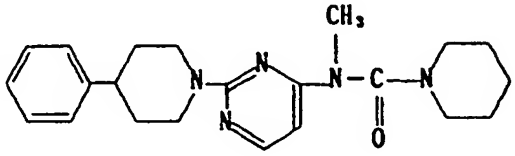
(2194) p-Toluenesulfonate of (2192)

(2198)



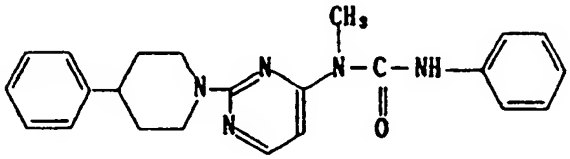
(2202) p-Toluenesulfonate of (2198)

(2206)



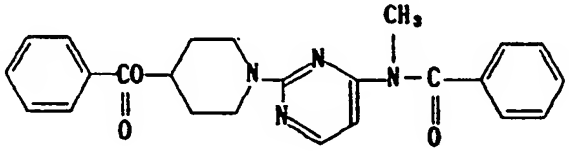
(2210) p-Toluenesulfonate of (2206)

(2214)



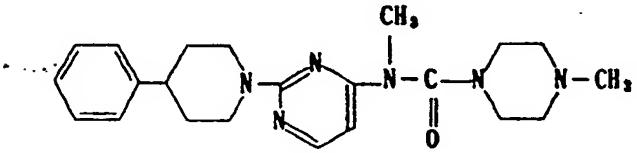
(2218) p-Toluenesulfonate of (2214)

(2222)



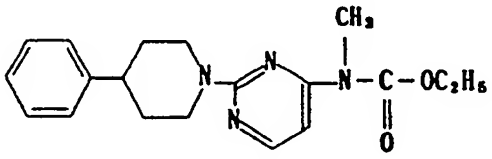
(2226) Hydrochloride of (2222)

(2230)



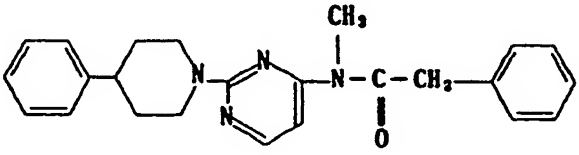
(2234) Di-p-toluenesulfonate of (2230)

(2238)



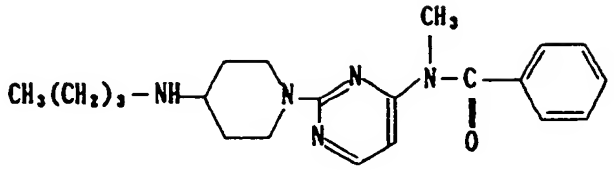
(2242) p-Toluenesulfonate of (2238)

(2246)



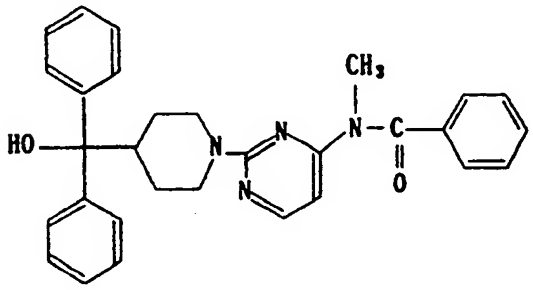
(2250) p-Toluenesulfonate of (2246)

(2254)



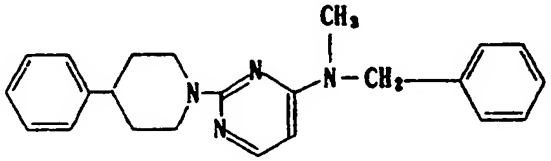
(2260) p-Toluenesulfonate of (2254)

(2264)



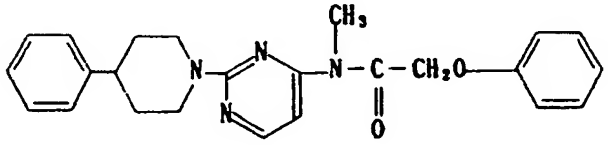
(2270) p-Toluenesulfonate of (2264)

(2274)



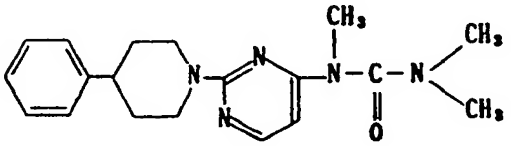
(2278) p-Toluenesulfonate of (2274)

(2282)



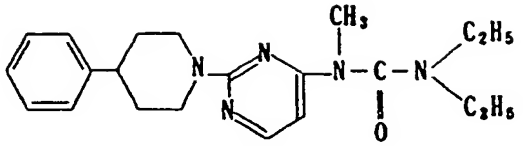
(2286) p-Toluenesulfonate of (2282)

(2290)



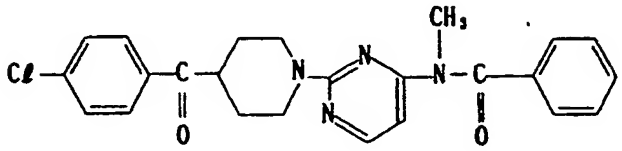
(2294) p-Toluenesulfonate of (2290)

(2298)



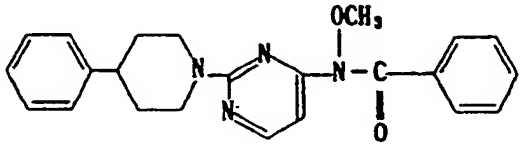
(2302) p-Toluenesulfonate of (2298)

(2306)



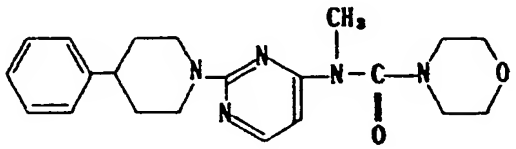
(2310) p-Toluenesulfonate of (2306)

(2314)



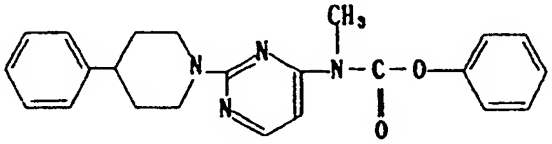
(2318) p-Toluenesulfonate of (2314)

(2322)



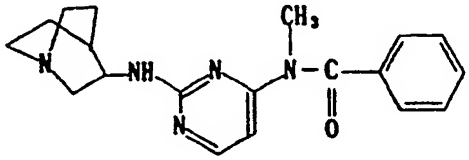
(2326) p-Toluenesulfonate of (2322)

(2330)



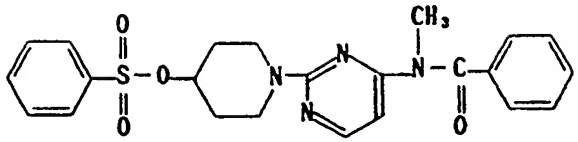
(2334) p-Toluenesulfonate of (2330)

(2338)



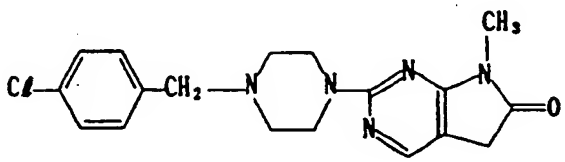
(2342) Dihydrochloride of (2338)

(2346)



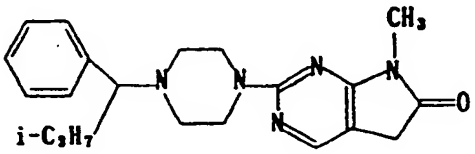
(2350) Hydrochloride of (2346)

(3100)



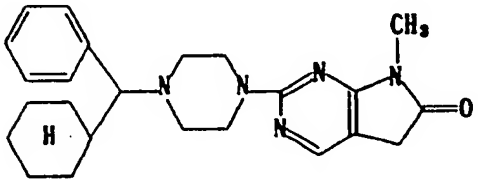
(3104) Hydrochloride of (3100)

(3108)

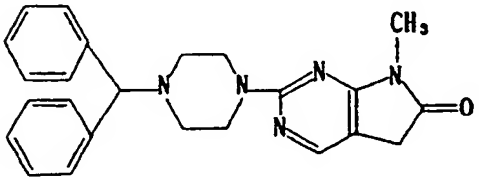


(3112) p-Toluenesulfonate of (3108)

(3116)

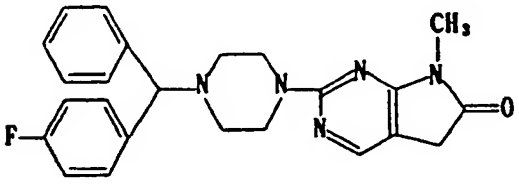


(3124)



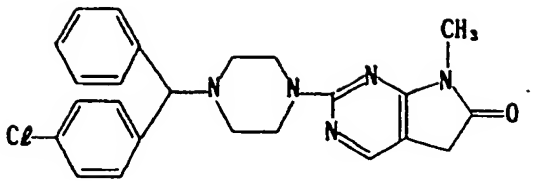
(3128) Hydrochloride of (3124)

(3132)



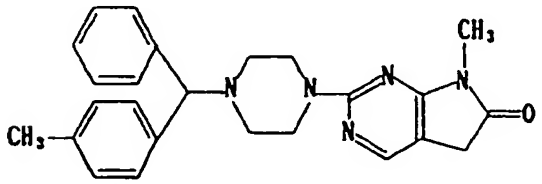
(3136) Hydrochloride of (3132)

(3140)



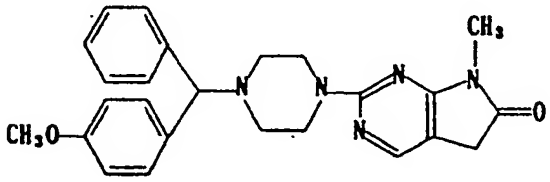
(3144) Hydrochloride of (3140)

(3148)

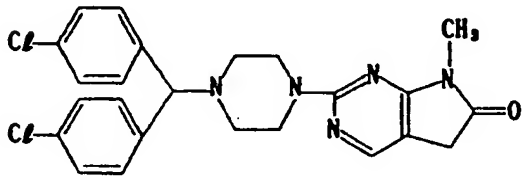


(3152) p-Toluenesulfonate of (3148)

(3156)

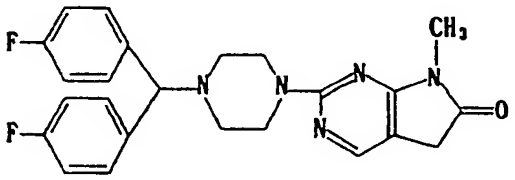


(3172)



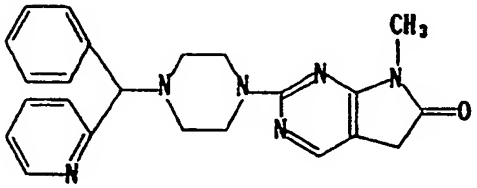
(3176) p-Toluenesulfonate of (3172)

(3180)



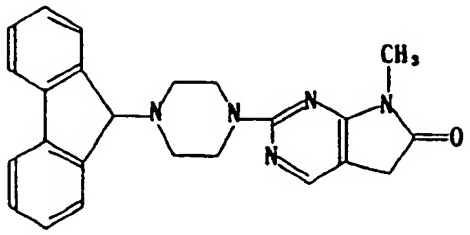
(3184) p-Toluenesulfonate of (3180)

(3188)



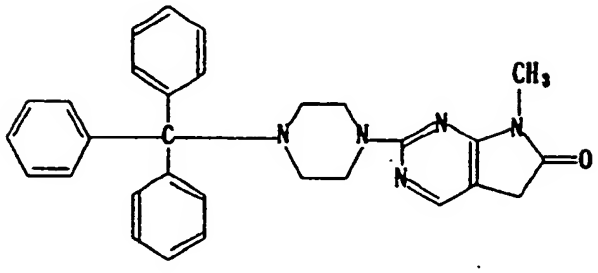
(3192) p-Toluenesulfonate of (3188)

(3196)

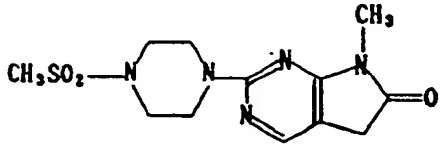


(3200) Hydrochloride of (3196)

(3300)

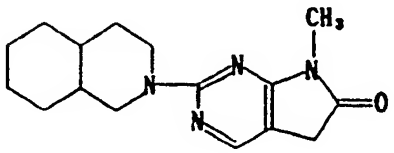


(3400)



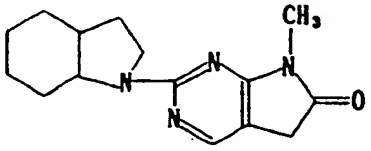
(3404) p-Toluenesulfonate of (3400)

(3408)



(3412) Hydrochloride of (3408)

(3416)

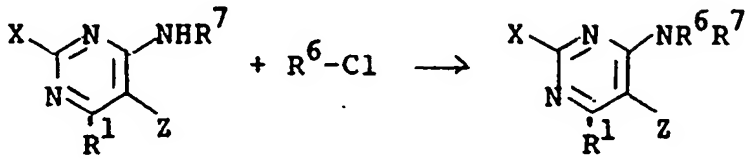


(3420) Hydrochloride of (3416)

The compounds of formulae (1), (2) and (3) may be produced by known methods, particularly the methods described in Japanese Laid-Open Patent Publication Nos. 140568/1986 and 87627/1986, or by treating the intermediates obtained by these methods in accordance with known methods (for example, the elimination of the protecting group by reduction). Examples 1 to 9 given hereinafter describe the production of these compounds in detail.

For example, compounds of formula (I) in which Y is and -NR^6R^7 and R^6 is other than hydrogen may be produced by the following reaction scheme 1.

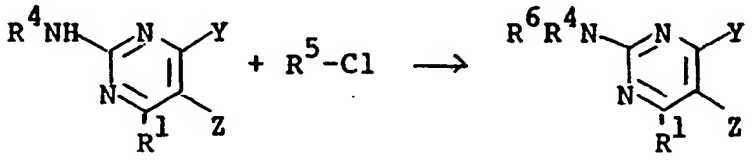
Reaction scheme 1



(II)

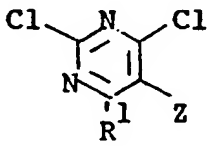
Compounds of general formula (1) in which X is -NR^4R^5 may be produced by the following reaction scheme 2.

Reaction scheme 2



(III)

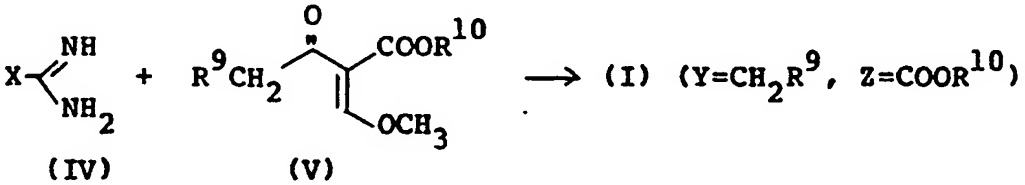
The starting compounds of formulae (II) and (III) in the reaction schemes 1 and 2 may be produced by the method described at J. Chem. Soc., 1965, pages 755-761, from



as a starting material. The reactions in the reaction schemes 1 and 2 are conveniently carried out at a temperature of 20 to 150 °C in a solvent such as toluene, dioxane, pyridine or water in the presence of, as required, a basic compound. The basic compound may conveniently be, for example, an organic base (such as triethylamine, pyridine and 4-dimethylaminopyridine), and an inorganic base (such as sodium carbonate and potassium carbonate).

Compounds of general formula (1) in which Y is CH_2R^3, R^3 is hydrogen or a lower alkyl group and Z is a lower alkoxycarbonyl group may be produced in accordance with the following reaction scheme 3.

Reaction scheme 3



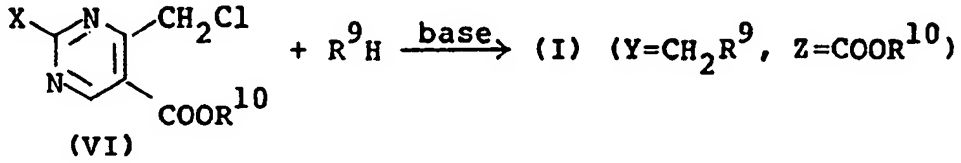
(IV) (V)

Specifically, by reacting compounds (IV) with (V) at a temperature of 20 to 100 °C in a reaction medium such as water, methanol, ethanol, THF and DMF, compounds of formula (I) In which Y = R^{10}, and

$Z = COOR^{13}$ are obtained.

Compounds of general formula (I) in which Y is CH_2R^9, R^9 is other than hydrogen and lower alkyl group and Z is a lower alkoxycarbonyl group may be produced in accordance with the reaction scheme 4.

Reaction scheme 4



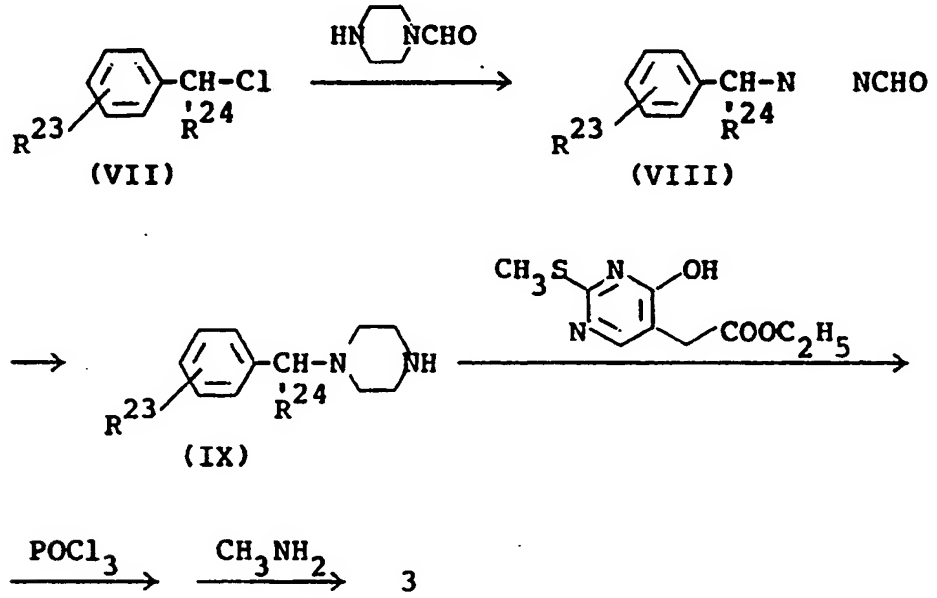
(VI)

Compound (VI) may be prepared in the same way as in [Production Method No. 7] of Japanese Laid-Open Patent Publication No. 65873/1986 except that X is used instead of benzylpiperazine. Compounds of formula (I) in which Y is CH_2R^9 and Z is $COOR^{10}$ are obtained by reacting compound (VI) with R^9H in the presence of an organic base and as pyridine or triethylamine, or an inorganic base such as potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, potassium hydride or sodium hydride in the presence of an inert solvent such as toluene or tetrahydrofuran or in the absence of solvent.

The compounds of general formula (2) can be synthesized by the same methods as in the synthesis of the compound of general formula (1).

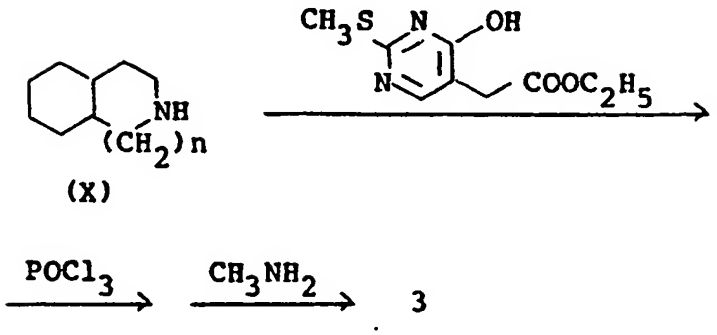
The compounds of general formula (3) can be produced by the methods shown in the following schemes 5 and 6.

Reaction scheme 5



The starting material (VII) may be produced by the method described in J. A. C. S., 71, 2731 (1949). The reaction of the compound (VII) with N-formylpiperazine in a solvent such as acetonitrile or dimethylformamide or in the absence of solvent, optionally in the presence of a basic compound, at a temperature of 20 to 150 °C, preferably 20 to 100 °C, to form the compound (VIII). An inorganic base such as sodium carbonate or potassium carbonate, or an organic base such as triethylamine or pyridine may be used as the basic compound. Compound (III) is then hydrolyzed in the presence of an acid or an alkali to yield compound (IV). The hydrolysis is carried out in a solvent such as water, methanol or ethanol at a temperature of 0 to 150 °C, preferably 20 to 100 °C.

Reaction scheme 6



Compounds of formula (3) are produced from compound (IV) or (X) in accordance with scheme 5 by known methods, particularly the methods described in Japanese Laid-Open Patent Publications Nos. 140568/1986 and 87627/1986 or by treating the intermediates obtained by these methods in accordance with known methods (for example, the reductive elimination of the protective group). Examples 7 to 9 given below illustrate the production of the compounds of formula (3) in detail.

Investigations of the present inventors show that the compounds of formulae (1), (2) and (3) are useful as therapeutic agents for treatment of neurological diseases.

The compounds of formulae (1), (2) and (3) are normally used in the form of a pharmaceutical composition, and are administered by various routes (e.g., oral, subcutaneous, intramuscular, intravenous, intrarhinal, skin permeation and through the rectum).

The present invention also embraces a pharmaceutical preparation comprising a compound of general formula (1), (2) or (3) or its pharmaceutically acceptable salt. The pharmaceutically acceptable salt includes, for example, acid addition salts and quaternary ammonium (or amine) salts.

Examples of the pharmaceutically acceptable salts of the compounds (1), (2) and (3) include salts formed from acids capable of forming pharmaceutically acceptable non-toxic acid-addition salts containing anions, such as hydrochlorides, hydrobromides, sulfates, bisulfites, phosphates, acid phosphates, acetates, maleates, fumarates, succinates, lactates, tartrates, benzoates, citrates, gluconates, glucanates, methanesulfonates, p-toluenesulfonates and naphthalenesulfonates or their hydrates, and quaternary ammonium (or amine) salts or their hydrates.

The composition of this invention may be formulated into tablets, capsules, powders, granules, troches, cachet wafer capsules, elixirs, emulsions, solutions, syrups, suspensions, aerosols, ointments, aseptic injectables, molded cataplasmas, tapes, soft and hard gelatin capsules, suppositories, and aseptic packed powders. Examples of the pharmaceutically acceptable carrier include lactose, glucose, sucrose, sorbitol, mannitol, corn starch, crystalline cellulose, gum arabic, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinyl pyrrolidone, tragacanth gum, gelatin, syrup, methyl cellulose, carboxymethyl cellulose, methylhydroxybenzoic acid esters, propylhydroxybenzoic acid esters, talc, magnesium stearates, inert polymers, water and mineral oils.

Both solid and liquid compositions may contain the aforesaid fillers, binders, lubricants, wetting agents, disintegrants, emulsifying agents, suspending agents, preservatives, sweetening agents and flavoring agents. The composition of this invention may be formulated such that after administration to a patient, the active compound is released rapidly, continuously or slowly.

In the case of oral administration, the compound of formula (1), (2) or (3) is mixed with a carrier or diluent and formed into tablets, capsules, etc. In the case of parenteral administration, the active ingredient is dissolved in a 10 % aqueous solution of glucose, isotonic salt water, sterilized water or a like liquid, and enclosed in vials or ampoules for intravenous instillation or injection or intramuscular injection. Advantageously, a dissolution aid, a local anesthetic agent, a preservative and a buffer may also be included into the medium. To increase stability, it is possible to lyophilize the present composition after introduction into a vial or ampoule. Another example of parenteral administration is the administration of the pharmaceutical composition through the skin as an ointment or a cataplasm. In this case, a molded cataplasm or a tape is advantageous.

The composition of this invention contains 0.1 to 2000 mg, more generally 0.5 to 1000 mg, of the active component for each unit dosage form.

The compound of formula (1), (2) or (3) is effective over a wide dosage range. For example, the amount

of the compound administered for one day usually falls within the range of 0.03 mg/kg to 100 mg/kg. The amount of the compound to be actually administered is determined by a physician depending, for example, upon the type of the compound administered, and the age, body weight, reaction condition, etc. of the patient and the administration route.

The above dosage range, therefore, does not limit the scope of the invention. The suitable number of administrations is 1 to 6, usually 1 to 4, daily.

The compound of formula (1), (2) or (3) by itself is an effective therapeutic agent for disorders of the peripheral nervous system and the central nervous system. If required, it may be administered in combination with at least one other equally effective drug. Examples of such an additional drug are gangliosides, mecobalamin and isaxonine.

The formulations of the compounds (1), (2) and (3) in accordance with this invention and their biological activities will be illustrated in detail by a series of Examples B and Examples given below. It should be understood however that they do not limit the scope of the invention. Each of the following examples showing the composition of the invention uses one of the compounds described hereinabove or one of other pharmaceutically active compounds encompassed within general formula (1), (2) and (3).

REFERENTIAL EXAMPLE 1

4-Methylamino-2-(4-phenylpiperidino)pyrimidine (compound No. 1024):-

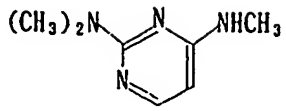
To a solution of 17.0 g (0.11 mole) of 2,4-dichloropyrimidine in 150 ml of dichloromethane was added methylamine (0.25 mole, 20 ml of 40 % methanol solution) at such a rate that the temperature of the solution was maintained at 5 °C. After the addition, the solution was stirred at room temperature for 12 hours. The reaction mixture was concentrated under reduced pressure, and extracted with dichloromethane. The dichloromethane layer was dried over an anhydrous sodium sulfate, and concentrated under reduced pressure to give 14.0 g (purity 80 %) of 2-chloro-4-methylaminopyrimidine.

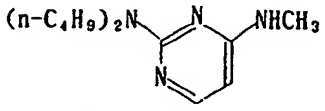
Two hundred milliliters of n-butanol was added to 3.0 g (0.02 mole) of 2-chloro-4-methylaminopyrimidine and 8.4 g (0.05 mole) of 4-phenylpiperidine, and the mixture was heated at 130 °C for 1 hour. The reaction mixture was concentrated under reduced pressure, and extracted with dichloromethane. The dichloromethane layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 4.0 g (yield 71 %) of the desired compound as an oil.

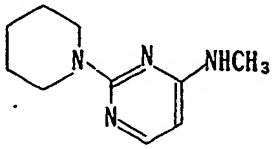
^{1}H-NMR spectrum (deuterochloroform, δ ppm):

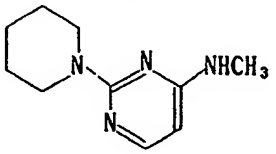
1.4-2.0(5H, m), 2.93(3H, d, J=5.2Hz), 2.6-3.1(2H, m), 4.60(1H, m), 4.92(2H, br. d, J=12.6Hz), 5.67(1H, d, J=7.2Hz), 7.28(5H, s), 7.93(1H, d, J=7.2 Hz).

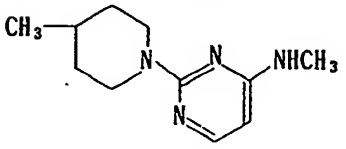
In a similar manner, the following compounds were produced.

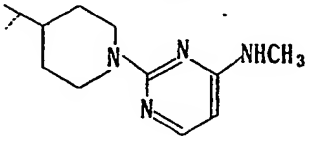
(1000) 

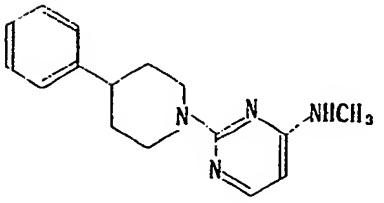
(1004) 

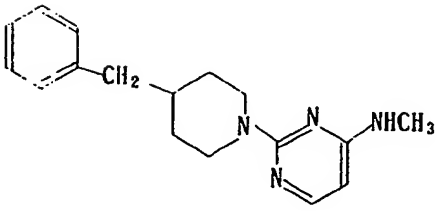
(1008) 

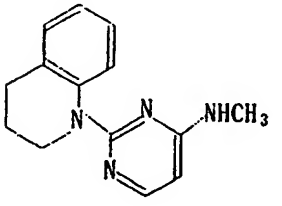
(1012) 

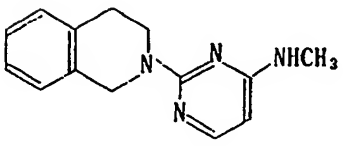
(1016) 

(1020) 

(1024) 

(1028) 

(1032) 

(1036) 

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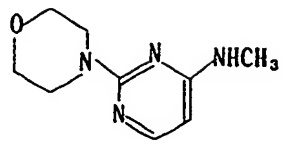

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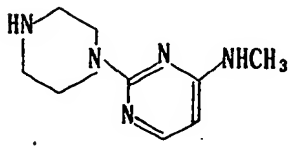

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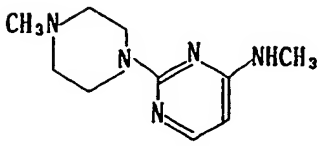

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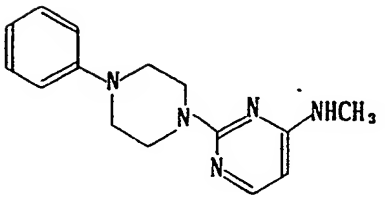

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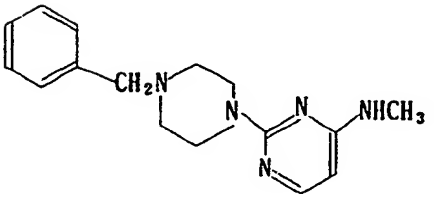

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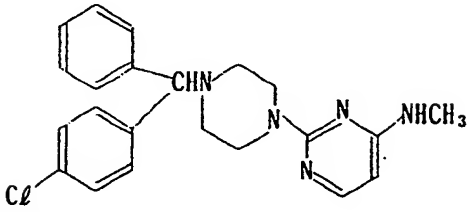

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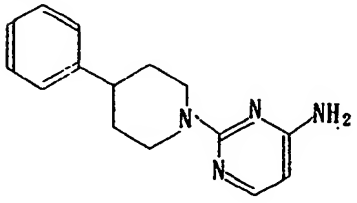

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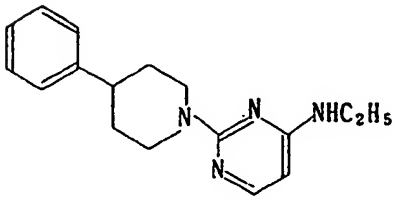

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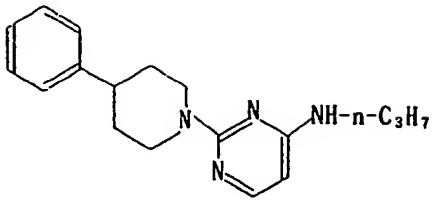

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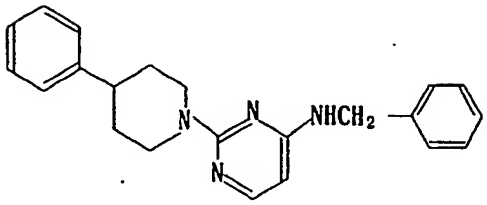

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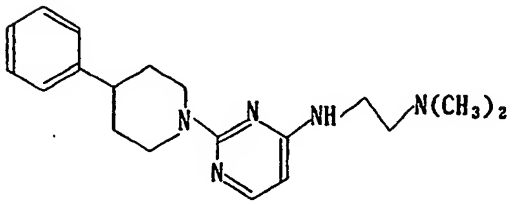

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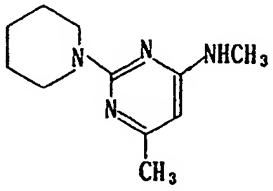

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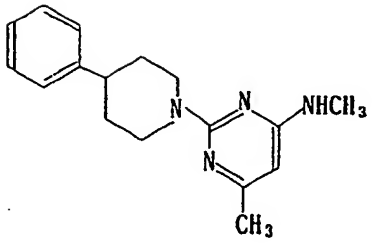

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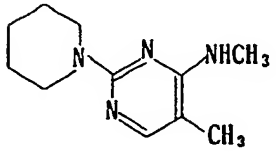

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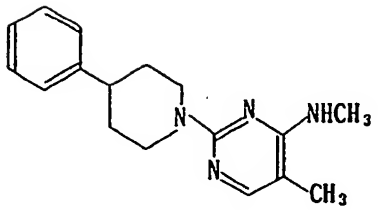

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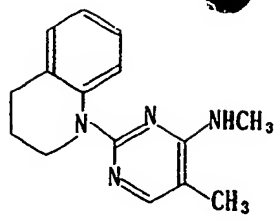

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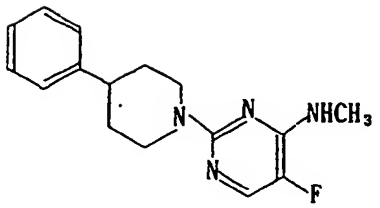

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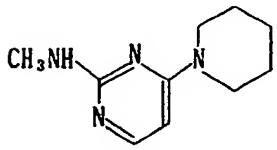

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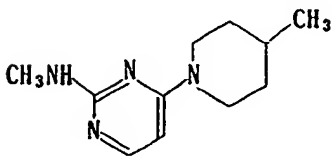

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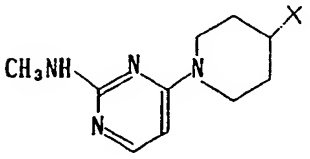

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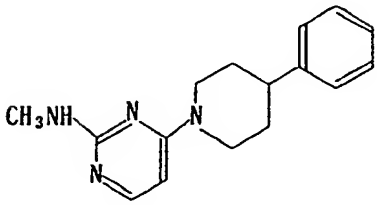
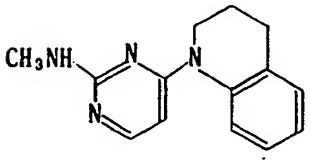


(1124)



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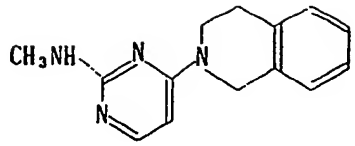
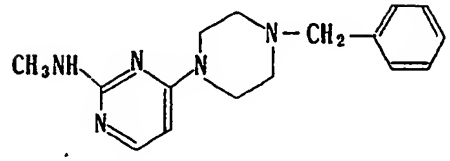
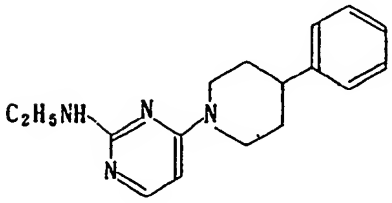


(1132)



(1136)



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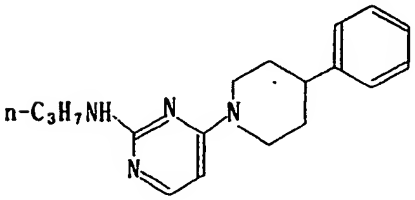

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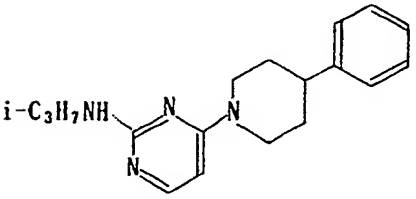
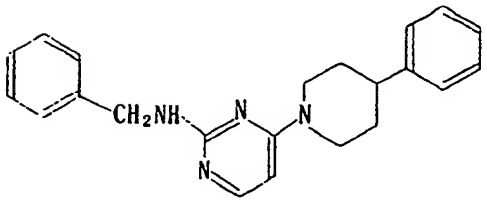
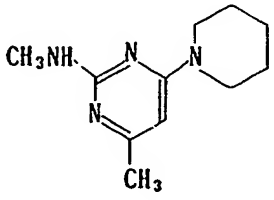


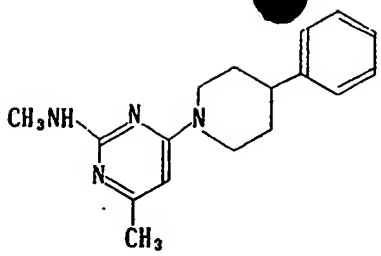
(1148)



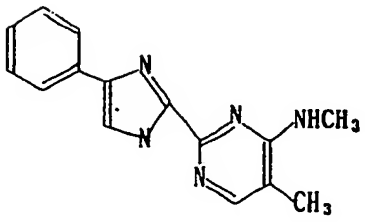
(1152)



(1156)



(1160)



The properties of the compounds (intermediate) are shown in Table 1 below.

Table 1

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
1000	51	Oil	2.90(3H, d, J=5.2Hz), 3.13(6H, s), 4.66(1H, m), 5.63(1H, d, J=5.2Hz), 7.88(1H, d, J=5.2Hz)
1004	29	Oil	0.92(6H, m), 1.0-1.8(8H, m), 2.88(3H, d, J=5.2Hz), 3.51(4H, m), 4.55(1H, m), 5.56(1H, d, J=5.2Hz), 7.84(1H, d, J=5.2Hz)
1008	68	Oil	1.92(4H, m), 2.88(3H, d, J=5.2Hz), 3.52(4H, m), 4.76(1H, m), 5.63(1H, d, J=5.2Hz), 7.88(1H, d, J=5.2Hz)
1012	95	Oil	1.62(6H, br. s), 2.92(3H, d, J=5.4Hz), 3.72(4H, br. s), 4.60(1H, m), 5.64(1H, d, J=6.0Hz), 7.90(1H, d, J=6.0Hz)
1016	72	Oil	0.95(3H, d, J=5.2Hz), 0.9-1.8(5H, m), 2.6-3.0(2H, m), 2.90(3H, d, J=5.2Hz), 4.69(2H, br. d, J=12.6Hz), 4.70(1H, m), 5.64(1H, d, J=5.2Hz), 7.89(1H, d, J=5.2Hz)
1020	62	Oil	0.9(9H, s), 1.0-1.9(5H, m), 2.5-3.0(2H, m), 2.90(3H, d, J=5.2Hz), 4.6(1H, m), 4.80(2H, br. d, J=12.6Hz), 5.64(1H, d, J=5.2Hz), 7.9(1H, d, J=5.2Hz)

- to be continued -

Table 1 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
1028	63	Oil	1.0-2.0(5H, m), 2.54(2H, d, J=5.2Hz), 2.4-3.0(2H, m), 2.87(3H, d, J=5.2Hz), 4.65(2H, m), 4.72(2H, br. d, J=12.6Hz), 5.62(1H, d, J=5.2Hz), 7.0-7.4(5H, m), 7.88(1H, d, J=5.2Hz)
1032	66	96-98	1.7-2.2(2H, m), 2.8(2H, t, J=7.2Hz) 2.89(3H, d, J=5.2Hz), 4.02(2H, t, J=7.2Hz), 4.70(1H, m), 5.82(1H, d, J=5.2Hz), 6.8-7.3(3H, m), 7.82(1H, d, J=7.2Hz), 7.99(1H, d, J=5.2Hz)
1036	77	Oil	2.92(5H, m), 4.02(2H, t, J=5.2Hz), 4.7(1H, m), 4.89(2H, s), 5.67(1H, d, J=7.2Hz), 7.18(4H, m), 7.94(1H, d, J=7.2Hz)
1040	60	Oil	2.89(3H, d, J=5.2Hz), 3.73(8H, s), 4.70(1H, m), 5.69(1H, d, J=5.2Hz), 7.88(1H, d, J=5.2Hz)
1048	56	Oil	2.32(3H, s), 2.43(4H, m), 2.88(3H, d, J=5.2Hz), 3.78(4H, m), 4.72(1H, m), 5.65(1H, d, J=5.2Hz), 7.86(1H, d, J=5.2Hz)
1052	56	120-122	2.91(3H, d, J=4Hz), 3.24(4H, m), 3.95(4H, m), 4.60(1H, m), 5.70(1H, d, J=5.4Hz), 6.8-7.4(5H, m), 7.92(1H, d, J=5.4Hz)

- to be continued -

Table 1 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
1056	68	Oil	2.48(4H, m), 2.87(3H, d, J=5.2Hz), 3.53(2H, s), 3.77(4H, m), 4.60(1H, m), 5.64(1H, d, J=5.2Hz), 7.32(5H, m), 7.87(1H, d, J=5.2Hz)
1060	80	Oil	2.42(4H, m), 2.85(3H, d, J=5.6Hz), 3.76(4H, m), 4.24(1H, s), 4.56(1H, m), 5.65(1H, d, J=5.6Hz), 7.0-7.5(9H, m), 7.88(1H, d, J=5.6Hz)
1064	61	Oil	1.4-2.2(4H, m), 2.5-3.1(3H, m), 4.62(2H, br. s), 4.88(2H, br. d, J=12.6Hz), 5.72(1H, d, J=5.2Hz), 7.25(5H, m), 7.94(1H, d, J=5.2Hz)
1068	58	Oil	1.24(3H, t, J=7.2Hz), 1.4-2.0(4H, m), 2.5-3.1(3H, m), 3.1-3.5(2H, m), 4.58(1H, m), 4.90(2H, br. d, J=12.6Hz), 5.65(1H, d, J=5.2Hz), 7.0-7.5(5H, m), 7.92(1H, d, J=5.2Hz)
1072	75	Oil	0.97(3H, t, J=7.2Hz), 1.4-2.1(6H, m), 2.5-3.1(3H, m), 3.24(2H, q, J=7.2Hz), 4.68(1H, br. s), 4.88(2H, br. d, J=12.6Hz), 5.65(1H, d, J=5.2Hz), 7.27(5H, m), 7.90(1H, d, J=5.2Hz)
1076	57	Oil	1.4-2.0(4H, m), 2.5-3.1(3H, m), 4.52(2H, d, J=5.2Hz), 4.90(2H, br. d, J=12.6Hz),

- to be continued -

Table 1 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
1076	57	Oil	4.91(1H, m), 5.68(1H, d, J=5.2Hz), 7.0-7.5(10H, m), 7.92(1H, d, J=5.2Hz)
1080	36	Oil	1.4-2.0(4H, m), 2.27(6H, s), 2.50(2H, m), 2.5-3.2(3H, m), 3.36(2H, m), 3.46(2H, s), 4.90(2H, br. d, J=12.6Hz), 5.24(1H, m), 5.67(1H, d, J=5.2Hz), 7.27(5H, m), 7.88(1H, d, J=5.2Hz)
1084	50	91-93	1.60(6H, br. s), 2.23(3H, s), 2.88(3H, d, J=5.2Hz), 3.75(4H, br. s), 4.50(1H, m), 5.54(1H, s)
1088	57	Oil	1.5-2.0(4H, m), 2.23(3H, s), 2.6-3.0(3H, m), 2.90(3H, d, J=5.2Hz), 4.51(1H, m), 4.96(2H, br. d, J=12.6Hz), 5.57(1H, s), 7.28(5H, s)
1092	21	Oil	1.60(6H, br. s), 1.88(3H, s), 3.0(3H, d, J=5.2Hz), 3.75(4H, br. s), 4.2(1H, br. s), 7.65(1H, s)
1096	75	Oil	1.4-2.0(4H, m), 1.92(3H, s), 2.5-3.1(3H, m), 3.02(3H, d, J=5.2Hz), 4.40(1H, m), 4.90(2H, br. d, J=12.6Hz), 7.28(5H, m), 7.68(1H, s)
1100	81	Oil	1.8-2.1(5H, m), 2.79(2H, t, J=7.2Hz), 2.99(3H, d, J=5.2Hz),

- to be continued -

Table 1 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
1100	81	Oil	4.03(2H, t, J=7.2Hz), 4.42(1H, m), 6.8-7.2(3H, m), 7.7-8.0(2H, m)
1104	48	121-124	1.4-2.1(4H, m), 2.5-3.1(3H, m), 3.02(3H, d, J=4.0Hz), 4.85(1H, m), 4.88(2H, br. d, J=12.6Hz), 7.28(5H, m), 7.75(1H, d, J=4.0Hz)
1112	24	117-118	0.96(3H, d, J=5.2Hz), 0.9-1.8(5H, m), 2.6-3.0(2H, m), 2.96(3H, d, J=5.2Hz), 4.32(2H, br. d, J=12.6Hz), 4.80(1H, m), 5.88(1H, d, J=5.2Hz), 7.87(1H, d, J=5.2Hz)
1116	16	179-180	0.89(9H, s), 1.0-1.9(5H, m), 2.5-3.0(2H, m), 2.95(3H, d, J=5.2Hz), 4.45(2H, br. d, J=12.6Hz), 4.75(1H, m), 5.89(1H, d, J=5.2Hz), 7.88(1H, d, J=5.2Hz)
1120	18	148-154	1.4-2.1(5H, m), 2.97(3H, d, J=5.2Hz), 2.6-3.1(2H, m), 4.53(2H, br. d, J=12.6Hz), 5.95(1H, d, J=7.2Hz), 7.28(5H, s), 7.88(1H, d, J=7.2Hz)
1124	20	175-176	1.8-2.1(2H, m), 2.76(2H, t, J=7.2Hz), 2.99(3H, d, J=5.2Hz), 3.96(2H, t, J=7.2Hz), 4.9(1H, m), 6.32(1H, d, J=5.2Hz), 6.9-7.5(4H, m), 7.88(1H, d, J=5.2Hz)

- to be continued -

Table 1 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
1128	19	123-126	2.90(5H, m), 3.83(2H, t, J=5.2Hz), 4.72(2H, s), 4.90(1H, m), 5.92(1H, d, J=7.2Hz), 7.19(4H, s), 7.92(1H, d, J=7.2Hz)
1132	17	-	2.47(4H, m), 2.92(3H, d, J=5.2Hz), 3.52(2H, s), 3.59(4H, m), 4.75(1H, m), 5.84(1H, d, J=5.2Hz), 7.31(5H, m), 7.85(1H, d, J=5.2Hz)
1136	17	158-160	1.24(3H, t, J=7.2Hz), 1.5-2.1(4H, m), 2.5-3.2(3H, m), 3.2-3.6(2H, m), 4.52(2H, br. d, J=12.6Hz), 4.70(1H, m), 5.92(1H, d, J=5.2Hz), 7.0-7.5(5H, m), 7.89(1H, d, J=5.2Hz)
1140	18	134-136	0.98(3H, t, J=7.2Hz), 1.4-2.1(6H, m), 2.6-3.1(3H, m), 3.35(2H, q, J=7.2Hz), 4.53(2H, br. d, J=12.6Hz), 4.80(1H, br. s), 5.93(1H, d, J=5.2Hz), 7.29(5H, m), 7.90(1H, d, J=5.2Hz)
1144	13	158-160	1.2(3H, s), 1.27(3H, s), 1.4-2.0(4H, m), 2.2-3.1(3H, m), 3.9-4.3(1H, m), 4.52(2H, br. d, J=12.6Hz), 4.65(1H, m), 5.9(1H, d, J=5.2Hz), 7.0-7.5(5H, m), 7.89(1H, d, J=5.2Hz)
1148	21	148-149	1.3-2.05(4H, m), 2.5-3.1(3H, m), 4.50(2H, br. d, J=12.6Hz), 4.60(2H, br. d, J=5.2Hz),

- to be continued -

Table 1 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
1148	21	148-149	5.35(1H, m), 5.95(1H, d, J=5.2Hz), 7.0-7.5(10H, m), 7.88(1H, d, J=5.2Hz)
1152	31	84-85	1.65(6H, br. s), 2.22(3H, s), 2.95(3H, d, J=5.2Hz), 3.57(4H, br. s), 4.75(1H, m), 5.77(1H, s)
1156	10	198-199	1.5-2.0(4H, m), 2.23(3H, s), 2.6-3.1(3H, m), 2.96(3H, d, J=5.2Hz), 4.4-4.8(3H, m), 5.83(1H, s), 7.26(5H, m)
1160	83	162-165	2.03(3H, s), 3.12(3H, d, J=5.2Hz), 4.90(1H, m), 7.2-7.5(3H, m), 7.85(3H, m), 8.12(1H, s), 8.6(1H, s)

REFERENTIAL EXAMPLE 2

4-Methylamino-2-(4-phenylpiperidino)pyrimidine maleate (compound No. 1026):-

A solution of 0.43 g (3.73 mmoles) of maleic acid in 10 ml of methanol was added to a solution of 1.0 g (3.73 mmoles) of 4-methylamino-2-(4-phenylpiperidino)pyrimidine in 10 ml of methanol, and the mixture was stirred at room temperature for 1 hour. The mixed solution was concentrated under reduced pressure and washed with ether to give 1.25 g (yield 87 %) of the desired product.

Melting point: 163-166 °C.

^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm):

1.6-2.2(4H, m), 2.6-3.3(5H, m), 3.04(3H, d, J=5.2Hz), 4.74(1H, br. d, J=12.6Hz), 6.30(1H, d, J=7.2Hz), 7.30(5H, m), 7.71(1H, d, J=7.2Hz), 8.40(1H, m).

Similarly, the folllowing compounds were produced.

(1014): maleate of (1012)
(1026): maleate of (1024)
(1034): maleate of (1032)
(1038): maleate of (1036)
(1086): maleate of (1084)
(1090): maleate of (1088)
(1094): maleate of (1092)
(1098): maleate of (1096)
(1102): maleate of (1100)

(1110): maleate of (1108)
(1122): maleate of (1120)
(1130) maleate of (1128)
(1158): maleate of (1156)
(1162): maleate of (1160)

The data of these compounds are given in Table 2 below.

Table 2

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
1014	89	164-165	1.70(6H, br. s), 3.02(3H, d, J=3.8Hz), 3.76(4H, br. s), 6.35(2H, s), 7.65(1H, m), 8.32(1H, m), 12.50(1H, m)
1034	94	42-46	1.9-2.3(2H, m), 2.79(2H, t, J=7.2Hz), 3.01(3H, d, J=5.2Hz), 4.0(2H, t, J=7.2Hz), 6.22(2H, s), 6.46(1H, d, J=5.2Hz), 7.20(3H, m), 7.50(1H, m), 7.76(1H, d, J=5.2Hz), 8.80(1H, m)
1038	77	149-151	2.9-3.2(5H, m), 4.0(2H, t, J=7.2Hz), 4.92(2H, s), 6.32(1H, d, J=7.2Hz), 6.36(2H, s), 7.25(4H, s), 7.75(1H, d, J=7.2Hz), 8.40(1H, m)
1086	99	155-157	1.68(6H, br. s), 2.28(3H, s), 3.0(3H, d, J=5.2Hz), 3.80(4H, br. s), 6.0(1H, s), 6.33(2H, s), 8.15(1H, m), 11.7(1H, m)
1090	91	151-154	1.5-2.2(4H, m), 2.29(3H, s), 2.6-3.3(6H, m), 4.81(2H, br. d, J=12.6Hz), 6.02(1H, s), 6.32(2H, s), 7.28(5H, br. s), 8.15(1H, m), 12.2(1H, m)
1094	91	150-152	1.70(6H, br. s), 2.04(3H, s), 3.08(3H, d, J=5.2Hz), 3.76(4H, br. s), 6.33(2H, s), 7.15(1H, m), 7.59(1H, s)

- to be continued -

Table 2 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
1098	92	163-165	1.6-2.2(4H, m), 2.03(3H, s), 2.6-3.3(3H, m), 3.09(3H, d, J=5.2Hz), 4.71(2H, br. d, J=12.6Hz), 6.33(2H, s), 7.0-7.4(5H, m), 7.60(1H, s)
1102	81	145-150	1.8-2.3(5H, m), 2.80(2H, t, J=5.2Hz), 3.08(3H, d, J=5.2Hz), 4.0(2H, t, J=5.2Hz), 6.25(2H, s), 7.1-7.6(4H, m), 7.70(1H, s)
1110	91	187-188	1.74(6H, br. s), 2.32(3H, s), 2.96(3H, d, J=5.2Hz), 3.5(2H, br. s), 3.95(2H, br, s), 5.83(1H, s), 6.33(2H, s), 9.10(1H, m), 13.8(1H, m)
1122	92	155-158	1.6-2.2(4H, m), 3.0(3H, d, J=5.2Hz) 2.7-3.5(3H, m), 4.10(1H, br. d, J=12.6Hz), 5.25(1H, br. d, J=12.6Hz), 6.12(1H, d, J=7.2Hz), 6.33(2H, s), 7.30(5H, m), 7.50(1H, d, J=7.2Hz), 9.0(1H, br. s)
1130	87	158-159	2.9-3.2(5H, d, J=5.2Hz), 3.79(1H, t, J=5.2Hz), 4.16(1H, t, J=5.2Hz), 4.70(1H, s), 5.20(1H, s), 6.15(1H, br. d, J=7.2Hz), 6.30(2H, s), 7.27(4H, s), 7.52(1H, d, J=7.2Hz), 9.1(1H, m)

- to be continued -

Table 2 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
1158	95	173-175	1.6-2.2(4H, m), 2.32(3H, s), 2.6-3.5(6H, m), 4.1(1H, m), 5.2(1H, m), 5.88(1H, s), 6.34(2H, s), 7.30(5H, br. s), 9.20(1H, m), 13.9(1H, m)
1162	74	179-180	2.11(3H, s), 3.11(3H, d, J=7.2Hz), 6.32(2H, s), 6.50(1H, m), 7.2-8.0(6H, m), 8.20(1H, s), 8.84(1H, s)

REFERENTIAL EXAMPLE 3

1-Diphenylmethylpiperazine:-

11.2 g (98 mmoles) of 1-formylpiperazine was added to 10 g (49 mmoles) of chlorodiphenylmethnae, and the solution was stirred at room temperature for 48 hours, and the mixture was extracted with water and methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography, and 8.9 g (31.9 mmoles) of the resulting formyl compound was dissolved in 100 ml of ethanol, and 6.5 g (64 mmoles) of conc. hydrochloric acid was added, and the solution was refluxed for 1 hour. Then, the solvent was evaporated under reduced pressure, and the residue was extracted with K_2CO_3/water/CH_2Cl_2. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to give 6.8 g (yield 55 %) of the desired product.
Melting point: 93-95 °C.
^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm):
2.33(4H, m), 2.87(4H, m), 4.19(1H, s), 7.1-7.5 (10H, m).

EXAMPLE 1

4-(N-methylbenzamino)-2-(4-phenylpiperidino)pyrimidine (compound No. 164):-

A solution of 5.2 g (0.037 mole) of benzoyl chloride in 50 ml of tetrahydrofuran was added at room temperature over 30 minutes to a solution of 9.0 g (0.034 mole) of 4-methylamino-2-(4-phenylpiperidino)-pyrimidine in 90 ml of tetrahydrofuran and 5 ml of triethylamine. TWo hours after the end of the addition, 1 ml of pyridine was added. The mixture was then stirred for 2 days. The reaction mixture was extracted with dichloromethane. The dicloromethane layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give 8.8 g (yield 70 %) of the desired compound as an oil.
^{1}H-NMR spectrum (deuterochloroform, δ ppm):

1.4-2.0(4H, m), 2.5-3.0(3H, m), 3.55(3H, s), 4.62(2H, br. d, J = 12.6Hz), 6.14(1H, d, J = 7.2Hz), 7.1-7.6(10H, m), 8.06(1H, d, J = 7.2Hz).

Data of compounds produced in the same way as above are shown in Table 3 below.

Table 3

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
100	48	Oil	3.0(6H, s), 3.52(3H, s), 6.04(1H, d, J=5.2Hz), 7.1-7.5(5H, m), 7.98(1H, d, J=5.2Hz)
108	30	Oil	0.93(6H, m), 1.0-1.7(8H, m), 3.2-3.65(4H, m), 3.50(3H, s), 6.04(1H, d, J=5.2Hz), 7.1-7.6(5H, m), 7.96(1H, d, J=5.2Hz)
116	41	Oil	1.92(4H, m), 3.38(4H, m), 3.53(3H, m), 6.0(1H, d, J=5.2Hz), 7.2-7.5(5H, m), 7.96(1H, d, J=5.2Hz)
124	63	Oil	1.67(6H, br. s), 2.35(3H, s), 3.38(3H, s), 3.78(4H, m), 6.52(1H, d, J=6.0Hz), 8.25(1H, d, J=6.0Hz)
132	55	Oil	1.55(6H, m), 3.53(3H, s), 3.56(4H, m), 6.08(1H, d, J=5.2Hz), 7.40(5H, m), 8.04(1H, d, J=5.2Hz)
140	71	Oil	1.92(3H, d, J=5.2Hz), 0.8-1.8(5H, m), 2.7(2H, m), 3.52(3H, s), 4.44(2H, br. d, J=12.6Hz), 6.08(1H, d, J=5.2Hz), 7.40(5H, m), 8.04(1H, d, J=5.2Hz)
148	34	Oil	0.88(9H, s), 1.0-1.8(5H, m), 2.63(2H, m), 3.53(3H, s), 4.55(2H, br. d, J=12.6Hz), 6.08(1H, d, J=5.2Hz), 7.2-7.7(5H, m), 8.05(1H, d, J=5.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
156	71	Oil	1.4-2.0(4H, m), 2.5-3.2(3H, m), 4.91(2H, br. d, J=12.6Hz), 7.0-7.7(7H, m), 7.90(2H, m), 8.32(2H, m)
172	20	Oil	1.33(3H, t, J=7.2Hz), 1.4-2.0(4H, m), 2.5-3.0(3H, m), 4.13(2H, q, J=7.2Hz), 4.64(2H, br. d, J=12.6Hz), 6.01(1H, d, J=5.2Hz), 7.0-7.7(10H, m,), 8.04(1H, d, J=5.2Hz)
180	37	Oil	0.98(3H, t, J=7.2Hz), 1.3-2.0(6H, m), 2.5-3.01(3H, m), 4.03(2H, t, J=7.2Hz), 4.63(2H, br. d, J=12.6Hz), 6.0(1H, d, J=5.2Hz), 7.1-7.6(10H, m), 8.04(1H, d, J=5.2Hz)
188	59	Oil	1.2-2.0(4H, m), 2.5-3.0(3H, m), 4.60(2H, br. d, J=12.6Hz), 5.28(2H, s), 5.95(1H, d, J=5.2Hz), 7.0-7.70(15H, m), 7.96(1H, d, J=5.2Hz)
196	60	Oil	1.2-2.0(4H, m), 2.56(6H, s), 2.5-3.10(5H, m), 4.36(2H, t, J=8Hz), 4.67(2H, br. d, J=12.6Hz), 6.0(1H, d, J=5.6Hz), 7.0-7.6(10H, m), 8.0(1H, d, J=5.6Hz)
204	28	Oil	1.5-2.1(4H, m), 2.35(3H, s), 2.6-3.2(3H, m), 3.40(3H, s), 4.90(2H, br. d, J=12.6Hz), 6.60(1H, d, J=12.6Hz), 7.28(5H, m), 8.28(1H, d, J=7.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
212	34	88-94	1.16(6H, d, J=7.2Hz), 1.4-2.1(4H, m), 2.6-3.3(4H, m), 3.36(3H, s), 4.88(2H, br. d, J=12.6Hz), 6.51(1H, d, J=5.2Hz), 7.24(5H, m), 8.24(1H, d, J=5.2Hz)
220	45	Oil	1.25(9H, s), 1.5-2.0(4H, m), 2.6-3.2(3H, m), 3.29(3H, s), 4.91(2H, br. d, J=12.6Hz), 6.50(1H, d, J=5.2Hz), 7.26(5H, m), 8.26(1H, d, J=5.2Hz)
228	35	Oil	1.0-2.1(14H, m), 2.6-3.2(4H, m), 3.36(3H, s), 4.90(2H, br. d, J=12.6Hz), 6.50(1H, d, J=5.2Hz), 7.25(5H, m), 8.25(1H, d, J=5.2Hz)
236	66	101-104	1.3-2.0(4H, m), 2.5-3.0(3H, m), 3.52(3H, s), 4.60(2H, br. d, J=12.6Hz), 6.11(1H, d, J=5.2Hz), 7.1-7.5(9H, m), 8.10(1H, d, J=5.2Hz)
244	33	Oil	1.2-2.0(4H, m), 2.5-3.0(3H, m), 3.51(3H, s), 4.56(2H, br. d, J=12.6Hz), 6.15(1H, d, J=5.2Hz), 7.0-7.5(9H, m), 8.10(1H, d, J=5.2Hz)
260	41	Oil	1.2-1.9(4H, m), 2.4-2.9(3H, m), 3.56(3H, s), 4.49(2H, br. d, J=12.6Hz), 6.16(1H, d, J=3.6Hz), 7.0-7.5(5H, m), 7.6(2H, d, J=9.5Hz), 8.16(1H, d, J=3.6Hz), 8.20(2H, d, J=9.5Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
268	27	Oil	1.4-2.0(4H, m), 2.5-3.0(3H, m), 3.55(3H, s), 3.79(3H, s), 4.72(2H, br. d, J=12.6Hz), 6.07(1H, d, J=5.2Hz), 6.81(2H, m), 7.1-7.6(7H, m), 8.05(1H, d, J=5.2Hz)
276	57	Oil	1.4-2.0(4H, m), 2.5-3.1(3H, m), 3.53(3H, s), 3.79(6H, s), 3.84(3H, s), 4.70(2H, br. d, J=12.6Hz), 6.13(1H, d, J=5.2Hz), 6.70(2H, s), 7.22(5H, m), 8.05(1H, d, J=5.2Hz)
292	44	Oil	1.5-2.0(4H, m), 2.6-3.1(3H, m), 3.55(3H, s), 4.77(2H, br. d, J=12.6Hz), 6.24(1H, d, J=5.2Hz), 6.44(1H, dd, J=3.2, 2.0Hz), 7.0(1H, dd, J=3.0, 1.0Hz), 7.1-7.5(6H, m), 8.16(1H, d, J=5.2Hz)
300	84	Oil	0.5-2.0(5H, m), 2.2-2.6(4H, m), 3.59(3H, s), 3.76(2H, br. d, J=12.6Hz), 6.06(1H, d, J=5.2Hz), 7.0-7.6(10H, m), 8.0(1H, d, J=5.2Hz)
308	35	Oil	2.37(3H, s), 2.95(2H, t, J=5.2Hz), 3.41(3H, s), 4.05(2H, t, J=5.2Hz), 4.92(2H, s), 6.64(1H, d, J=5.2Hz), 7.22(4H, s), 8.32(1H, d, J=5.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
316	96	Oil	1.85-2.20(2H, m), 2.33(3H, s), 2.80(2H, t, J=5.2Hz), 3.40(3H, s), 4.04(2H, t, J=5.2Hz), 6.93(1H, d, J=5.2Hz), 6.95-7.30(3H, m), 7.72(1H, dd, J=7.2, 2.0Hz), 8.34(1H, d, J=5.2Hz)
324	79	Oil	1.6-2.1(2H, m), 2.76(2H, t, J=5.2Hz), 3.52(3H, s), 3.80(2H, t, J=5.2Hz), 6.39(1H, d, J=5.2Hz), 6.9-7.7(9H, m), 8.15(1H, d, J=5.2Hz)
332	42	Oil	3.52(3H, s), 3.59(8H, m), 6.18(1H, d, J=5.2Hz), 7.36(5H, m), 8.04(1H, d, J=5.2Hz)
340	33	Oil	2.18(1H, s), 2.79(4H, m), 3.51(3H, s), 3.56(4H, m), 6.12(1H, d, J=5.2Hz), 7.35(5H, m), 8.02(1H, d, J=5.2Hz)
348	19	Oil	2.31(3H, s), 2.36(4H, m), 3.52(3H, s), 3,60(4H, m), 6.12(1H, d, J=5.2Hz), 7.1-7.5(5H, m), 8.01(1H, d, J=5.2Hz)
356	72	Oil	3.10(4H, m), 3.56(3H, s), 3.76(4H, m), 6.20(1H, d, J=5.4Hz), 6.90(3H, m), 7.1-7.6(7H, m), 8.09(1H, d, J=5.4Hz)
364	52	Oil	2.36(4H, m), 3.4-3.8(9H, m), 6.11(1H, d, J=5.2Hz), 7.1-7.6(10H, m), 8.01(1H, d, J=5.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
372	50	58-62	2.32(4H, m), 3.49(3H, s), 3.62(4H, m), 4.23(1H, s), 6.13(1H, d, J=5.2Hz), 7.0-7.6(14H, m), 8.02(1H, d, J=5.2Hz)
380	63	Oil	1.65(6H, br. s), 2.29(3H, s), 2.35(3H, s), 3.34(3H, s), 3.77(4H, m), 6.32(1H, s)
388	64	Oil	1.5-2.11(4H, m), 2.32(3H, s), 2.37(3H, s), 2.6-3.1(3H, m), 3.36(3H, s), 4.92(2H, br. d, J=12.6Hz), 6.40(1H, s), 7.28(5H, br. s)
396	52	Oil	1.3-2.0(4H, m), 2.22(3H, s), 2.5-3.0(3H, m), 3.53(3H, s), 4.64(2H, br. d, J=12.6Hz), 6.05(1H, s), 7.1-7.6(10H, m)
404	49	Oil	1.3-1.8(6H, m), 1.89(3H, s), 3.40(3H, s), 3.63(4H, m), 7.1-7.5(5H, m), 8.0(1H, s)
412	28	Oil	1.5-2.1(4H, m), 2.0(3H, s), 2.08(3H, s), 2.6-3.2(3H, m), 3.20(3H, s), 4.85(2H, br. d, J=12.6Hz), 7.27(5H, m), 8.26(1H, s)
420	54	Oil	1.4-1.9(4H, m), 1.94(3H, s), 2.5-3.05(3H, m), 3.42(3H, s), 4.71(2H, br. d, J=12.6Hz), 7.0-7.6(10H, m), 8.05(1H, s)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
428	55	Oil	1.3-2.1(4H, m), 2.5-3.0(3H, m), 3.51(3H, d, J=0.5Hz), 4.60(1H, br. d, J=12.6Hz), 7.0-7.6(10H, m), 8.0(1H, d, J=2Hz)
600	67	Oil	1.2-1.7(6H, m), 3.12(4H, m), 3.61(3H, s), 6.09(1H, d, J=7.2Hz), 7.1-7.5(5H, m), 8.0(1H, d, J=7.2Hz)
608	57	Oil	0.5-1.0(2H, m), 0.87(3H, d, J=5.2Hz), 1.3-1.7(3H, m), 2.3-2.7(2H, m), 3.61(3H, s), 3.5-3.9(2H, br. d, J=12.6Hz), 6.10(1H, d, J=7.2Hz), 7.1-7.5(5H, m), 8.0(1H, d, J=7.2Hz)
616	55	143-145	0.84(9H, s), 0.9-1.6(5H, m), 2.44(2H, m), 3.61(3H, s), 3.87(2H, br. d, J=12.6Hz). 6.10(1H, d, J=5.2Hz), 7.2-7.5(5H, m), 8.0(1H, d, J=5.2Hz)
624	67	Oil	1.0-1.9(4H, m), 2.4-2.9(3H, m), 3.64(3H, s), 3.95(2H, br. d, J=12.6Hz), 6.16(1H, d, J=5.2Hz), 7.0-7.55(10H, m), 8.07(1H, d, J=5.2Hz)
632	67	Oil	1.35(3H, t, J=7.2Hz), 1.0-1.9(4H, m), 2.4-2.9(3H, m), 3.97(2H, br. d, J=12.6Hz), 4.22(2H, q, J=7.2Hz), 6.15(1H, d, J=7.2Hz), 7.0-7.6(10H, m), 8.05(1H, d, J=7.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
640	52	Oil	0.99(3H, t, J=7.2Hz), 1.0-2.0(6H, m), 2.4-2.9(3H, m), 3.99(2H, br. d, J=12.9Hz), 4.0-4.3(2H, m), 6.15(1H, d, J=7.2Hz), 7.0-7.6(10H, m), 8.04(1H, d, J=7.2Hz)
648	63	Oil	1.0-2.0(4H, m), 1.46(3H, s), 1.54(3H, s), 2.5-3.0(3H, m), 4.15(2H, br. d, J=12.6Hz), 5.13(1H, m), 6.19(1H, d, J=7.2Hz), 7.0-7.6(10H, m), 8.04(1H, d, J=7.2Hz)
658	88	Oil	1.0-1.85(4H, m), 2.4-2.80(3H, m), 3.95(2H, br. d, J=12.6Hz), 5.38(2H, s), 6.10(1H, d, J=5.2Hz), 7.0-7.60(15H, m), 7.98(1H, d, J=5.2Hz)
664	71	160-162	1.0-2.0(4H, m), 2.4-2.9(3H, m), 3.62(3H, s), 3.99(2H, br. d, J=12.6Hz), 6.16(1H, d, J=5.2Hz), 7.0-7.5(9H, m), 8.05(1H, d, J=5.2Hz)
672	60	153-154	1.0-2.0(4H, m), 2.5-2.9(3H, m), 3.65(3H, s), 4.0(2H, br. d, J=12.6Hz), 6.20(1H, d, J=7.2Hz), 7.0-7.5(5H, m), 7.56(2H, d, J=10.8Hz), 8.01(1H, d, J=7.2Hz), 8.14(2H, d, J=10.8Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
680	59	Oil	1.4-2.0(4H, m), 2.5-3.0(3H, m), 3.56(3H, s), 4.22(2H, br. d, J=12.6Hz), 6.25(1H, d, J=5.2Hz), 6.36(1H, dd, J=4.0, 1.0Hz), 6.88(1H, d, J=4.0Hz), 7.0-7.5(6H, m), 8.08(1H, d, J=5.2Hz)
688	41	Oil	0.8-1.8(5H, m), 2.3-2.8(4H, m), 3.51(3H, s), 4.45(2H, br. d, J=12.6Hz), 6.07(1H, d, J=5.2Hz), 7.0-7.6(10H, m), 8.02(1H, d, J=5.2Hz)
696	69	99-101	2.0(2H, m), 2.48(3H, s), 2.79(2H, t, J=5.2Hz), 3.48(3H, s), 3.97(2H, t, J=5.2Hz), 6.80(1H, d, J=5.2Hz), 7.0-7.5(4H, m), 8.13(1H, d, J=5.2Hz)
252	38	Oil	1.3-2.0(4H, m), 2.4-3.0(3H, m), 3.47(3H, s), 4.59(2H, br. d, J=12.6Hz), 6.47(1H, d, J=5.2Hz), 7.0-7.6(9H, m), 8.13(1H, d, J=5.2Hz)
284	38	136-138	1.2-2.0(4H, m), 2.4-3.0(3H, m), 3.53(3H, s), 4.59(2H, br. d, J=12.6Hz), 6.15(1H, d, J=5.2Hz), 6.95-7.60(14H, m), 8.05(2H, d, J=5.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
137	95	Oil	0.88(3H, d, J=7Hz), 1.1-2.8(7H, m), 3.50(3H, s), 4.28(2H, m), 6.03(1H, d, J=5Hz), 7.34(5H, m), 7.99(1H, d, J=5Hz)
145	38	Oil	0.7-2.8(12H, m), 3.49(3H, s), 4.40(2H, m), 6.02(1H, d, J=5Hz), 7.32(5H, m), 7.96(1H, d, J=5Hz)
147	96	Oil	0.88(6H, d, J=7Hz), 1.0-2.9(8H, m), 3.50(3H, s), 4.47(2H, m), 6.04(1H, d, J=5Hz), 7.34(5H, m), 8.00(1H, d, J=5Hz)
153	38	Oil	1.04(3H, d, J=7Hz), 1.54(6H, m), 2.76(1H, m), 3.49(3H, s), 4.28(1H, m), 4.70(1H, m), 6.02(1H, d, J=5Hz), 7.32(5H, m), 7.98(1H, d, J=5Hz),
171-2	56	126-129	1.2-2.0(4H, m), 2.32(3H, s), 2.5-3.0(3H, m), 3.52(3H, s), 4.65(2H, br. d, J=12.6Hz), 6.08(1H, d, J=5.2Hz), 6.98-7.42(9H, m), 8.01(1H, d, J=5.2Hz)
2000	95	Oil	0.87(6H, d, J=7Hz), 1.1-3.4(6H, m), 3.50(3H, s), 4.36(2H, m), 6.06(1H, d, J=5Hz), 7.36(5H, m), 8.02(1H, d, J=5Hz)
2008	50	Oil	1.4-2.0(4H, m), 2.38(3H, s), 2.5-3.1(3H, m), 3.44(3H, s), 4.75(2H, br. d, J=12.6Hz), 6.80(1H, d, J=5.2Hz), 7.0-7.4(7H, m), 7.66(2H, d, J=7.2Hz), 8.09(1H, d, J=5.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2048	37	Oil	8.00(1H, d, J=5Hz), 7.2-7.5(5H, m), 6.12(1H, d, J=5Hz), 4.4-4.7(2H, m), 3.50(3H, s), 1.1-3.0(17H, m)
2056	89	Oil	8.00(1H, d, J=5Hz), 7.2-7.5(5H, m), 6.08(1H, d, J=5Hz), 3.7-4.3(4H, m), 3.50(3H, s), 2.9-3.3(2H, m), 1.0-2.0(4H, m)
2064	47	Oil	8.00(1H, d, J=5Hz), 7.2-7.6(5H, m), 6.18(1H, d, J=5Hz), 4.2-4.5(2H, m), 3.60(3H, s), 1.0-4.0(12H, m)
2074	35	Oil	8.12(2H, d, J=7Hz), 7.88(1H, d, J=5Hz), 7.35(1H, d, J=7Hz), 6.22(1H, d, J=5Hz), 7.2-7.6(5H, m), 4.8-5.0(2H, m), 3.64(3H, s), 2.7-3.1(2H, m), 1.1-2.0(5H, m)
2080	16	Oil	8.02(1H, d, J=7Hz), 7.2-7.6(5H, m), 6.29(1H, d, J=7Hz), 4.0-4.6(2H, m), 2.49(3H, s), 0.8-3.2(14H, m)
2088	38	Oil	8.03(1H, d, J=7Hz), 7.2-7.5(5H, m), 6.28(1H, d, J=7Hz), 3.47(3H, s), 3.08(3H, s), 1.6-3.8(10H, m)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2096	36	Oil	8.03(1H, d, J=5Hz), 7.2-7.6(5H, m), 6.58(1H, d, J=5Hz), 4.5-4.8(2H, m), 4.18(2H, q, J=7Hz), 1.50(3H, s), 1.5-3.0(7H, m), 1.30(3H, t, J=2Hz)
2112	95	Oil	0.96(6H, s), 1.26(4H, m), 3.48(3H, s), 3.50(4H, m), 6.02(1H, d, J=5Hz), 7.32(5H, m), 7.98(1H, d, J=5Hz)
2120	44	Oil	0.85(3H, t, J=7Hz), 1.47(4H, m), 2.79(2H, m), 3.1-3.7(6H, m), 6.08(1H, d, J=5Hz), 7.30(10H, m), 8.04(1H, d, J=5Hz)
2128	28	Oil	1.4-2.1(4H, m), 2.5-3.1(3H, m), 3.54(3H, s), 4.73(2H, br. d, J=12.6Hz), 6.24(1H, d, J=5.4Hz), 6.92(1H, dd, J=5.4, 3.6Hz), 7.0-7.5(7H, m), 8.08(1H, d, J=5.4Hz)
2136	93	Oil	1.3-2.0(4H, m), 2.45-3.0(3H, m), 3.52(3H, s), 4.48(2H, br. d, J=12.6Hz), 6.13(1H, d, J=5.4Hz), 7.0-7.4(6H, m), 7.75(1H, m), 8.10(1H, d, J=5.4Hz), 8.54(2H, m)
2144	53	Oil	8.00(1H, d, J=7Hz), 7.2-7.5(5H, m), 6.13(1H, d, J=7Hz), 4.3-4.5(2H, m), 2.0-3.8(7H, m), 3.10(6H, s), 3.36(3H, s)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2152	40	Oil	8.00(1H, d, J=7Hz), 7.2-7.5(5H, m), 6.38(1H, d, J=7Hz), 3.38(3H, s), 4.0-4.8(2H, m), 0.8-2.04(14H, m)
2160	45	Oil	8.00(1H, d, J=5Hz), 7.2-7.6(5H, m), 6.10(1H, d, J=5Hz), 4.1-4.4(2H, m), 3.58(3H, s), 1.0-3.5(10H, m)
2170	42	Oil	1.2-3.1(7H, m), 3.51(3H, s), 3.89(1H, m), 4.40(2H, m), 6.19(1H, d, J=5Hz), 7.2-7.9(10H, m), 8.01(1H, d, J=5Hz)
2178	85	Oil	1.5-3.1(6H, m), 3.51(3H, s), 3.90(1H, m), 4.74(2H, m), 6.02(1H, d, J=5Hz), 6.50(2H, d, J=8Hz), 7.24(7H, m), 7.96(1H, d, J=8Hz)
2184	56	Oil	($CDCl_3$-CD_3OD) 1.2-3.3(7H, m), 3.50(3H, s), 4.46(2H, m), 6.20(1H, d, J=5Hz), 7.36(5H, m), 8.01(1H, d, J=5Hz)
2192	50	Oil	1.4-3.3(6H, m), 3.56(3H, s), 4.2-4.7(3H, m), 6.60(1H, d, J=7Hz), 7.1-7.9(14H, m), 7.96(1H, d, J=7Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2198	42	Oil	($CDCl_3$-CD_3OD) 1.4-3.3(7H, m), 3.53(3H, s), 4.42(2H, m), 6.72(1H, d, J=7Hz), 7.3-7.9(10H, m), 7.98(1H, d, J=7Hz)
2206	45	Oil	1.61(6H, br. s), 1.4-2.1(4H, m), 2.55-3.15(3H, m), 3.22(3H, s), 3.40(4H, br. s), 4.87(2H, br. d, J=12.6Hz), 5.97(1H, d, J=5.2Hz), 7.24(5H, m), 8.0(1H, d, J=5.2Hz)
2214	26	131-132	1.5-2.2(4H, m), 2.5-3.3(3H, m), 3.40(3H, s), 4.80(2H, br. d, J=12.6Hz), 6.16(1H, d, J=5.2Hz), 6.89-7.65(10H, m), 8.20(1H, d, J=5.2Hz), 12.23(1H, br,s)
2222	60	46-49	7.9-8.1(3H, m), 7.2-7.6(8H, m), 6.10(1H, d, J=5Hz), 5.0-5.2(1H, m), 3.8-4.1(2H, m), 3.50(3H, s), 1.8-2.0(6H, m)
2230	97	Oil	1.26-2.10(4H, m), 2.30(3H, s), 2.39(4H, m), 2.5-3.20(3H, m), 3.21(3H, s), 3.47(4H, m), 4.85(2H, br. d, J=12.6Hz), 5.96(1H, d, J=5.2Hz), 7.20(5H, m), 8.0(1H, d, J=5.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2238	69	Oil	1.35(3H, t, J=7.2Hz), 1.4-2.15(4H, m), 2.55-3.20(3H, m), 3.44(3H, s), 4.25(2H, q, J=7.2Hz), 4.86(2H, br. d, J=12.6Hz), 7.23(6H, m), 8.12(1H, d, J=5.2Hz)
2246	13	Oil	1.2-3.4(7H, m), 3.56(3H, s), 3.92(2H, s), 4.74(2H, m), 6.50(1H, d, J=7Hz), 7.18(10H, m), 8.18(1H, d, J=7Hz)
2254	45	Oil	0.94(3H, t, J=7Hz), 1.52(6H, m), 2.02(2H, m), 2.79(4H, m), 3.50(3H, s), 4.50(2H, m), 5.04(2H, m), 6.09(1H, d, J=7Hz), 7.36(5H, m), 7.98(1H, d, J=7Hz)
2264	90	Oil	1.1-1.6(4H, m), 2.4-2.9(3H, m), 3.46(3H, s), 4.50(2H, m), 6.06(1H, d, J=5Hz), 7.28(15H, m), 7.94(1H, d, J=5Hz)
2274	62	112-115	1.35-2.10(4H, m), 2.50-3.10(3H, m), 3.0(3H, s), 4.74(2H, s), 4.88(2H, br. d, J=12.6Hz), 5.79(1H, d, J=5.2Hz), 7.22(10H, m), 7.90(1H, d, J=5.2Hz)
2282	67	Oil	1.45-2.15(4H, m), 2.55-3.20(3H, m), 3.40(3H, s), 4.82(2H, br. d, J=12.6Hz), 5.05(2H, s), 6.37(1H, d, J=5.2Hz), 6.70-7.10(3H, m), 7.10-7.45(7H, m), 8.25(1H, d, J=5.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2290	42	Oil	1.4-2.1(4H, m), 2.96(6H, s), 2.58-3.20(3H, m), 3.20(3H, s), 4.85(2H, br. d, J=12.6Hz), 5.92(1H, d, J=5.2Hz), 7.22(5H, m), 8.02(1H, d, J=5.2Hz)
2298	56	Oil	1.15(6H, m), 1.4-2.1(4H, m), 2.5-3.2(3H, m), 3.18(3H, s), 3.35(4H, m), 4.88(2H, br. d, J=12.6Hz), 5.90(1H, d, J=5.2Hz), 7.22(5H, m), 7.98(1H, d, J=5.2Hz)
2306	75	Oil	1.76(4H, m), 2.92(2H, m), 3.36(1H, m), 3.51(3H, s), 4.52(2H, m), 6.52(1H, d, J=7Hz), 7.39(7H, m), 7.86(2H, d, J=7Hz), 8.02(1H, d, J=7Hz)
2314	26	Oil	1.2-2.0(4H, m), 2.1-2.9(3H, m), 3.90(3H, s), 4.32(2H, m), 6.70(1H, d, J=7Hz), 7.0-7.7(10H, m), 8.23(1H, d, J=7Hz)
2322	77	Oil	1.4-2.1(4H, m), 2.5-3.4(3H, m), 3.24(3H, s), 3.57(8H, m), 4.88(2H, br. d, J=12.6Hz), 6.0(1H, d, J=5.4Hz), 7.23(5H, m), 8.04(1H, d, J=5.4Hz)
2330	59	119-121	1.4-2.1(4H, m), 2.6-3.2(3H, m), 3.61(3H, s), 4.89(2H, br. d, J=12.6Hz), 7.0-7.5(11H), 8.16(1H, d, J=5.4Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2338	23	Oil	8.02(1H, d, J=7Hz), 7.2-7.6(5H, m), 6.38(1H, d, J=7Hz), 3.36(3H, s), 1.0-3.5(13H, m)
2346	54	Oil	8.00(1H, d, J=7Hz), 7.2-7.9(10H, m), 6.48(1H, d, J=7Hz), 4.2-4.5(2H, m), 3.38(3H, s), 1.4-3.8(7H, m)
2016	50	Oil	1.4-2.0(4H, m), 2.5-3.0(3H, m), 3.53(3H, s), 4.21(2H, br. d, J=12.6Hz), 6.12(1H, d, J=7.2Hz), 6.35(1H, d, J=7.2Hz), 7.0-7.5(11H, m)
2024	36	Oil	1.4-2.0(4H, m), 2.5-3.1(3H, m), 3.54(3H, s), 4.25(2H, br. d, J=12.6Hz), 7.0-7.6(10H, m), 7.41(1H, s). 7.79(1H, s)
2032	69	76-82	1.2-2.0(8H, m), 2.4-3.9(6H, m), 3.56(3H, s), 4.50(4H, m), 7.0-7.52(15H, m)
2040	28	Oil	1.4-2.1(4H, m), 2.5-3.2(3H, m), 3.50(3H, s), 4.38(2H, br. d, J=12.6Hz), 6.32(1H, dd, J=3.6, 2.0Hz), 6.71(1H, dd, J=3.0, 1.0Hz), 7.24(6H, m), 7.58(1H, s), 7.93(1H, s)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
154-1	61	Oil	1.4-2.2(4H, m), 2.6-3.2(3H, m), 3.36(3H, s), 3.43(3H, s), 4.43(2H, s), 4.84(2H, br. d, J=12.6Hz), 6.44(1H, d, J=5.2Hz), 7.22(5H, m), 8.22(1H, d, J=5.2Hz)
171-4	64	Oil	1.37(3H, t, J=7.2Hz), 1.4-2.1(4H, m), 2.5-3.05(3H, m), 3.52(3H, s), 3.98(2H, q, J=7.2Hz), 4.69(2H, br. d, J=12.6Hz), 6.03(1H, d, J=5.2Hz), 6.76(2H, m), 7.0-7.6(7H, m), 8.0(1H, d, J=5.2Hz)
297	60	Oil	1.80(4H, m), 2.90(3H, m), 4.92(2H, m), 6.64(1H, d, J=5Hz), 7.20(5H, m), 7.80(4H, m), 8.39(1H, d, J=5Hz)
305	90	Oil	1.76(4H, m), 2.90(2H, m), 3.40(1H, m), 3.51(3H, s), 4.49(2H, m), 6.11(1H, d, J=5Hz), 7.40(8H, m), 7.92(2H, m), 8.01(1H, d, J=5Hz)
307	19	Oil	8.01(1H, d, J=7Hz), 7.2-7.6(5H, m), 6.10(1H, d, J=7Hz), 4.2-4.4(2H, m), 1.2-3.8(10H, m), 3.35(3H, s)
241	69	Oil	1.1-2.1(4H, m), 2.5-3.0(3H, m), 3.50(3H, s), 4.60(2H, br. d, J=12.6Hz), 6.04(1H, d, J=5.2Hz), 6.8-7.7(9H, m), 8.04(1H, d, J=5.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2022	84	Oil	1.4-2.0(4H, m), 2.45-3.0(3H, m), 3.52(3H, s), 4.20(2H, br. d, J=12.6Hz), 6.10(1H, d, J=7.2Hz), 6.35(1H, d, J=7.2Hz), 7.0-7.4(10H, m)
2023	85	112-114	1.3-2.1(4H, m), 2.5-3.2(3H, m), 3.47(3H, s), 4.35(2H, br. d, J=12.6Hz), 6.31(1H, d, J=7.2Hz), 6.50(1H, d, J=7.2Hz), 6.65-7.6(9H, m, J=7.2Hz)
149	87	103-105	0.5-1.8(5H, m), 0.88(3H, d, J=5.2Hz), 2.3-2.8(2H, m), 4.15(2H, br. d, J=12.6Hz), 6.06(1H, d, J=5.2Hz), 7.1-7.8(10H, m), 8.08(1H, d, J=5.2Hz)
171-8	79	Oil	1.2-2.0(4H, m), 2.4-3.0(3H, m), 3.52(3H, s), 4.51(2H, br. d, J=12.6Hz), 6.32(1H, d, J=5.2Hz), 6.76-7.65(9H, m), 8.1(1H, d, J=5.2Hz)
171-10	62	Oil	1.2-2.1(4H, m), 2.5-3.0(3H, m), 3.49(3H, s), 4.53(2H, br. d, J=12.6Hz), 6.36(1H, d, J=5.2Hz), 7.0-7.5(8H, m), 8.12(1H, d, J=5.2Hz)
171-1	26	Oil	1.3-2.1(4H, m), 2.5-3.0(3H, m), 3.47(3H, s), 4.85(2H, d, J=12.6Hz), 6.35(1H, d, J=5.2Hz), 6.90(1H, d, J=15.4Hz), 7.0-7.6(10H, m), 7.65(1H, d, J=15.4Hz), 8.20(1H, d, J=5.2Hz)

- to be continued -

Table 3 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
171-6	41	Oil	1.4-2.0(4H, m), 2.34(3H, s), 2.5-3.0(3H, m), 3.46(3H, s), 4.64(2H, br. d, J=12.6Hz), 6.32(1H, d, J=5.2Hz), 7.0-7.4(9H, m), 8.04(1H, d, J=5.2Hz)
171-12	71	113-116	1.1-2.1(4H, m), 2.4-3.0(3H, m), 3.49(3H, s), 4.51(2H, br. d, J=12.6Hz), 6.1(1H, d, J=5.2Hz), 7.0-7.7(8H, m), 8.1(1H, d, J=5.2Hz)

EXAMPLE 2

4-(N-methylbenzamino)-2-(4-phenylpiperidino)pyrimidine p-toluenesulfonate (compound No. 168):-

A solution of 3.0 g (0.022 mole) of p-toluenesulfonic acid monohydrate in 300 ml of ethyl acetate was slowly added at room temperature to a solution of 6.0 g (0.022 mole) of 4-(N-methylbenzamino)-2-(4-phenylpiperidino)pyrimidine in 100 ml of ethyl acetate. As soon as the addition was effected, a suspension was formed. After the end of the addition, the suspension was stirred for 10 minutes. The resulting solid was separated by filtration, washed with ethyl acetate and ether, and dried to give 6.8 g (yield 83 %) of the desired compound.

Melting point: 180-182 °C.

^{1}H-NMR spectrum (deuterochloroform, δ ppm):

1.4-2.1(4H, m), 2.35(3H, s), 2.6-3.3(3H, m), 3.56(3H, s), 4.55(2H, br. d, J=12.6 Hz), 6.60(1H, d, J=7.2 Hz), 7.0-7.9(14H, m), 8.36 (1H, d, J=7.2Hz).

In the same way as above, the following compounds were produced and thier data are shown in Table 4.

Table 4

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
104	100	54-58	2.33(3H, s), 2.8-3.5(6H, m), 3.50(3H, s), 6.64(1H, d, J=7.2Hz) 7.13(2H, d, J=7.2Hz), 7.50(5H, m,), 7.75(2H, d, J=7.2Hz) 8.24(1H, d, J=7.2Hz)
112	100	Oil	0.90(6H, m), 1.0-1.8(8H, m), 2.35(3H, s), 3.2-3.7(4H, m), 3.5(3H, s), 6.58(1H, d, J=7.2Hz), 7.13(2H, d, J=7.2Hz), 7.3-7.7(5H, m), 7.76(2H, d, J=7.2Hz) 8.36(1H, d, J=7.2Hz)
120	82	125-126	2.0(4H, m), 2.35(3H, s), 3.44(2H, m), 3.52(3H, s), 3.72(2H, m), 6.56(1H, d, J=7.2Hz), 7.15(2H, d, J=7.2Hz), 7.2-7.7(5H, m), 7.78(2H, d, J=7.2Hz), 8.22(1H, d, J=7.2Hz)
128	90	149-150	1.72(6H, br. s), 2.37(3H, s), 2.48(3H, s), 3.50(3H, s), 3.84(4H, br. s), 7.18(2H, d, J=7.5Hz), 7.44(1H, d, J=7.2Hz), 7.81(2H, d, J=7.5Hz), 8.38(1H, d, J=7.2Hz)
136	79	48-52	1.63(6H, br. s), 2.36(3H, s), 3.52(3H, s), 3.64(4H, br, s), 6.56(1H, d, J=7.2Hz), 7.16(2H, d, J=7.2Hz), 7.55(5H, m), 7.79(2H, d, J=7.2Hz), 8.30(1H, d, J=7.2Hz)
144	90	49-51	0.94(3H, d, J=5.2Hz), 0.8-1.90(5H, m), 2.36(3H, s),

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
144	90	49-51	2.8-3.2(2H, m), 3.52(3H, s), 4.32(2H, br. d, J=12.6Hz), 6.6(1H, d, J=7.2Hz), 7.16(2H, d, J=7.2Hz), 7.3-7.7(5H, m), 7.8(2H, d, J=7.2Hz), 8.3(1H, d, J=7.2Hz)
152	72	52-56	0.85(9H, s), 1.0-2.0(5H, m), 2.36(3H, s), 2.5-3.2(2H, m), 3.52(3H, s), 4.44(2H, br. d, J=12.6Hz), 6.58(1H, d, J=7.2Hz), 7.16(2H, d, J=7.2Hz), 7.3-7.7(5H, m), 7.8(2H, d, J=7.2Hz) 8.28(1H, d, J=7.2Hz)
160	80	206-207	1.3-2.1(4H, m), 2.32(3H, s), 2.5-3.3(3H, m), 4.76(2H, br. d, J=12.6Hz), 7.0-8.4(16H, m)
176	75	68-72	1.36(3H, t, J=7.2Hz), 1.4-2.1(4H, m), 2.33(3H, s), 2.5-3.3(3H, m), 4.12(2H, q, J=7.2Hz), 4.42(2H, br. d, J=12.6Hz), 6.34(1H, d, J=7.2Hz), 7.0-7.9(12H, m), 8.32(1H, d, J=7.2Hz)
184	85	53-57	1.0(3H, t, J=7.2Hz), 1.4-2.1(6H, m) 2.35(3H, s), 2.5-3.3(3H, m), 4.04(2H, m), 4.42(2H, br. d, J=12.6Hz), 6.28(1H, d, J=7.2Hz), 7.0-7.7(14H, m), 8.35(1H, d, J=7.2Hz)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
192	80	59-62	1.2-2.0(4H, m), 2.31(3H, s), 2.5-3.2(3H, m), 4.34(2H, m), 5.28(2H, s), 6.33(1H, d, J=7.2Hz), 7.0-7.8(19H, m), 8.25(1H, d, J=7.2Hz)
200	79	98-105	1.4-2.0(4H, m), 2.32(6H, s), 2.5-3.2(3H, m), 2.92(3H, s), 2.98(3H, s), 2.98(3H, s), 3.50(2H, m), 4.40(2H, br. d, J=12.6Hz), 4.60(2H, m), 6.40(1H, d, J=5.2Hz), 7.0-7.8(18H, m), 8.10(1H, d, J=5.2Hz), 10.80(1H, m)
208	90	172-174	1.6-2.2(4H, m), 2.35(3H, s), 2.48(3H, s), 2.6-3.5(3H, m), 3.52(3H, s), 4.77(2H, br. d, J=12.6Hz), 7.1-7.9(10H, m), 8.42(1H, d, J=7.2Hz)
216	86	154-156	1.24(6H, d, J=7.0Hz), 1.4-2.2(4H, m), 2.32(3H, s), 2.6-3.4(4H, m), 3.51(3H, s), 4.75(2H, br. d, J=12.6Hz), 7.12(2H, d, J=7.2Hz), 7.20(5H, m), 7.36(1H, d, J=7.2Hz), 7.76(2H, d, J=7.2Hz), 8.34(1H, d, J=7.2Hz)
224	86	158-160	1.40(9H, s), 1.5-2.2(4H, m), 2.34(3H, s), 2.6-3.3(3H, m), 3.38(3H, s), 4.76(2H, br. d, J=12.6Hz), 6.56(1H, d, J=7.2Hz), 7.0-7.4(7H, m), 7.82(2H, d, J=7.2Hz) 8.30(1H, d, J=7.2Hz)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
232	100	49-52	1.0-2.3(14H, m), 2.33(3H, s), 2.6-3.5(4H, m), 3.48(3H, s), 4.75(2H, br. d, J=12.6Hz), 7.12(2H, d, J=7.2Hz), 7.0-7.5(6H, m), 7.76(2H, d, J=7.2Hz), 8.32(1H, d, J=7.2Hz)
240	77	132-134	1.4-2.1(4H, m), 2.36(3H, s), 2.6-3.3(3H, m), 3.55(3H, s), 4.52(2H, br. d, J=12.6Hz), 6.67(1H, d, J=7.2Hz), 7.16(2H, d, J=7.2Hz), 7.0-7.7(9H, m), 7.81(2H, d, J=7.2Hz), 8.44(1H, d, J=7.2Hz)
248	84	168-170	1.2-2.1(4H, m), 2.32(3H, s), 2.5-3.4(3H, m), 3.51(3H, s), 4.48(2H, br. d, J=12.6Hz), 6.69(1H, d, J=7.2Hz), 7.12(2H, d, J=7.2Hz), 7.0-7.65(9H, m), 7.76(2H, d, J=7.2Hz), 8.40(1H, d, J=7.2Hz)
264	95	189-190	1.2-2.0(4H, m), 2.34(3H, s), 2.5-3.3(3H, m), 3.55(3H, s), 4.40(2H, br. d, J=12.6Hz), 6.85(1H, d, J=7.2Hz), 7.0-7.5(7H, m), 7.77(4H, d, J=7.2Hz), 8.31(2H, d, J=7.2Hz), 8.52(1H, d, J=7.2Hz)
272	84	56-60	1.4-2.0(4H, m), 2.33(3H, s), 2.6-3.25(3H, m), 3.54(3H, s), 3.84(3H, s), 4.65(2H, br. d, J=12.6Hz),

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
272	84	56-60	6.38(1H, d, J=7.2Hz), 6.92(2H, d, J=8.5Hz), 7.23(7H, m), 7.59(2H, d, J=8.5Hz), 7.80(2H, d, J=7.2Hz), 8.22(1H, d, J=7.2Hz)
280	91	174-76	1.4-2.2(4H, m), 2.32(3H, s), 2.5-3.4(3H, m), 3.51(3H, s), 3.86(6H, s), 3.91(3H, s), 4.65(2H, br. d, J=12.6Hz), 6.69(1H, d, J=7.2Hz), 6.85(2H, s), 7.0-7.4(7H, m), 7.76(2H, s), 8.30(1H, d, J=7.2Hz)
296	91	174-78	1.4-2.2(4H, m), 2.35(3H, s), 2.6-3.3(3H, m), 3.58(3H, s), 4.69(2H, br. d, J=12.6Hz), 6.55(1H, d, J=7.2Hz), 6.60(1H, m), 7.0-7.5(8H, m), 7.56(1H, m), 7.8(2H, d, J=7.2Hz), 8.36(1H, d, J=7.2Hz)
304	100	54-58	0.8-2.0(5H, m), 2.33(3H, s), 2.51(2H, d, J=7.2Hz), 2.6-3.2(2H, m), 3.49(3H, s), 4.35(2H, br. d, J=12.6Hz), 6.57(1H, d, J=7.2Hz), 7.0-7.9(14H, m), 8.28(1H, d, J=7.2Hz),
312	78	182-184	2.37(3H, s), 2.51(3H, s), 3.01(2H, t, J=5.2Hz), 3.57(3H, s), 4.04(2H, t, J=5.2Hz), 4.95(2H, s), 7.20(2H, d, J=7.2Hz), 7.25(4H, s), 7.54(1H, d, J=7.2Hz), 7.94(2H, d, J=7.2Hz), 8.40(1H, d, J=7.2Hz)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
320	81	49-51	1.9-2.3(2H, m), 2.36(3H, s), 2.40(3H, s), 2.72(2H, t, J=5.2Hz), 3.38(3H, s), 4.04(2H, t, J=5.2Hz), 7.20(5H, m), 7.50(1H, m), 7.76(3H, m), 8.53(1H, d, J=5.2Hz)
328	75	136-138	2.04(2H, q, J=5.2Hz), 2.38(3H, s), 2.73(2H, t, J=5.2Hz), 3.43(3H, s), 3.99(2H, t, J=5.2Hz), 6.88(1H, d, J=7.2Hz), 7.20(5H, m), 7.50(6H, m), 7.80(2H, d, J=7.2Hz), 8.50(1H, d, J=7.2Hz)
336	100	58-62	2.36(3H, s), 3.52(3H, s), 3.68(8H, br. s), 6.69(1H, d, J=7.0Hz) 7.15(2H, d, J=7.2Hz), 7.52(5H, m), 7.75(2H, d, J=7.2Hz), 8.28(1H, d, J=7.0Hz)
344	100	164-168	2.39(3H, s), 3.10(4H, m), 3.48(3H, s), 3.83(4H, m), 6.28(1H, d, J=5.2Hz), 7.20(2H, d, J=7.2Hz), 7.35(5H, m), 7.73(2H, d, J=7.2Hz), 8.05(1H, d, J=5.2Hz),
352	100	58-60	2.36(3H, s), 2.83(3H, s), 2.98(4H, m), 3.49(3H, s), 3.90(4H, m), 6.33(1H, d, J=5.2Hz), 7.15(2H, d, J=7.2Hz), 7.0-7.5(5H, m), 7.75(2H, d, J=7.2Hz), 8.06(1H, d, J=5.2Hz)
360	100	52-56	2.34(3H, s), 3.32(4H, br. s), 3.49(3H, s), 4.0(4H, br. s), 6.68(1H, d, J=7.2Hz),

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
360	100	52-56	7.0-7.8(14H, m), 8.22(1H, d, J=7.2Hz)
368	82	66-72	2.38(3H, s), 3.05(4H, m), 3.46(3H, s), 4.0(4H, m), 4.25(2H, s), 6.32(1H, d, J=5.2Hz), 7.17(2H, d, J=7.2Hz), 7.40(10H, m), 7.79(2H, d, J=7.2Hz), 8.05(1H, d, J=5.2Hz)
376	91	120-125	2.36(3H, s), 2.94(4H, m), 3.44(3H, s), 4.0(4H, m), 5.0(1H, m) 6.40(1H, d, J=5.2Hz), 7.0-7.9(18H, m), 8.05(1H, d, J=5.2Hz)
384	80	157-158	1.67(6H, br. s), 2.31(3H, s), 2.46(3H, s), 2.71(3H, s), 3.48(3H, s), 3.76(4H, m), 6.33(1H, s), 7.14(2H, d, J=7.2Hz), 7.80(2H, d, J=7.2Hz)
392	85	159-161	1.6-2.2(4H, m), 2.34(3H, s), 2.48(3H, s), 2.71(3H, s), 2.7-3.4(3H, m), 3.50(3H, s), 4.87(2H, br. d, J=12.6Hz), 7.14(2H, d, J=7.2Hz), 7.30(6H, m), 7.80(2H, d, J=7.2Hz)
400	94	60-65	1.4-2.1(4H, m), 2.32(3H, s), 2.64(3H, s), 2.6-3.3(3H, m), 3.52(3H, s), 4.64(2H, br. d, J=12.6Hz), 6.51(1H, s), 7.15(2H, d, J=7.2Hz), 7.0-7.7(10H, m), 7.80(2H, d, J=7.2Hz)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
408	83	50-55	1.64(6H, br. s), 2.04(3H, d, J=1.0Hz), 2.39(3H, s), 3.48(3H, s), 3.70(4H, br. s), 7.20(2H, d, J=7.2Hz), 7.52(5H, m), 7.80(2H, d, J=7.2Hz), 8.33(1H, s)
416	80	58-62	1.6-2.2(4H, m), 2.09(3H, m), 2.29(3H, s), 2.35(3H, s), 2.6-3.5(3H, m), 3.36(3H, s), 4.79(2H, br. d, J=12.6Hz), 7.18(2H, d, J=7.2Hz), 7.30(5H, m), 7.84(2H, d, J=7.2Hz), 8.46(1H, s),
424	94	68-72	1.4-2.2(4H, m), 2.06(3H, s), 2.35(3H, s), 2.6-3.4(3H, m), 3.49(3H, s), 4.62(2H, br. d, J=12.6Hz), 7.0-7.7(12H, m), 7.81(2H, d, J=8.5Hz), 8.37(1H, s)
432	80	146-148	1.3-2.2(4H, m), 2.36(3H, s), 2.5-3.4(3H, m), 3.58(3H, d, J=1.0Hz), 4.56(2H, br. d, J=12.6Hz), 7.0-7.9(14H, m), 8.44(1H, d, J=5.2Hz)
604	100	44-48	1.2-1.8(6H, m), 2.36(3H, s), 3.28(4H, m), 3.64(3H, s), 6.50(1H, dd. J=7.2, 1.5Hz), 7.20(2H, d, J=7.2Hz), 7.2-7.6(5H, m), 7.85(2H, d, J=7.2Hz) 8.39(1H, d, J=7.2Hz)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
612	100	44-48	0.5-1.1(2H, m), 0.89(3H, d, J=5.2Hz), 1.4-1.8(3H, m), 2.36(3H, s), 2.3-2.9(2H, m), 3.64(3H, s), 3.85(2H, br. d, J=12.6Hz), 6.53(1H, d, J=7.2Hz), 7.19(2H, d, J=7.2Hz), 7.2-7.6(5H, m), 7.84(2H, d, J=7.2Hz), 8.36(1H, d, J=7.2Hz)
620	84	106-110	0.82(9H, s), 0.9-1.8(5H, m), 2.0-3.0(2H, m), 2.36(3H, s), 3.61(3H, s), 4.0(2H, br. d, J=12.6Hz), 6.72(1H, d, J=7.2Hz), 7.18(2H, d, J=7.2Hz), 7.2-7.6(5H, m), 7.84(2H, d, J=7.2Hz), 8.42(1H, d, J=7.2Hz)
628	84	160-161	1.0-2.0(4H, m), 2.35(3H, s), 2.4-3.2(3H, m), 3.64(3H, s), 4.05(2H, br. d, J=12.6Hz), 6.72(1H, d, J=7.2Hz), 7.0-7.6(12H, m), 7.84(2H, d, J=7.2Hz), 8.49(1H, d, J=7.2Hz)
636	83	143-147	1.30(3H, t, J=7.2Hz), 1.0-2.0(4H, m), 2.35(3H, s), 2.4-3.3(3H, m), 4.10(2H, br. d, J=12.6Hz), 4.17(2H, q, J=7.2Hz), 6.80(1H, d, J=7.2Hz) 7.0-7.6(12H, m), 7.84(2H, d, J=7.2Hz), 8.48(1H, d, J=7.2Hz)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
644	96	178-180	0.95(3H, t, J=7.2Hz), 1.4-2.1(6H, m), 2.37(3H, s), 2.5-3.3(3H, m), 3.9-4.3(4H, m), 6.67(1H, d, J=7.2Hz), 7.0-8.0(14H, m), 8.55(1H, d, J=7.2Hz)
652	87	66-68	1.0-2.0(4H, m), 1.44(3H, s), 1.52(3H, s), 2.36(3H, s), 2.5-3.3(3H, m), 3.9-4.5(2H, m), 4.76(1H, m), 6.78(1H, d, J=7.2Hz), 7.0-7.7(12H, m), 7.83(2H, d, J=7.2Hz), 8.39(1H, d, J=7.2Hz)
660	91	116-120	1.2-2.0(4H, m), 2.33(3H, s), 2.4-3.2(3H, m), 4.04(2H, br. d, J=12.6Hz), 5.36(2H, s), 6.56(1H, d, J=7.2Hz), 6.9-7.9(19H, m), 8.38(1H, d, J=7.2Hz)
668	82	173-175	0.9-2.0(4H, m), 2.35(3H, s), 2.4-3.3(3H, m), 3.6(3H, s), 4.12(2H, br. d, J=12.6Hz), 6.82(1H, d, J=7.2Hz) 7.0-7.9(13H, m), 8.45(1H, d, J=7.2Hz)
676	79	199-200	1.0-2.0(4H, m), 2.36(3H, s), 2.5-3.2(3H, m), 3.64(3H, s), 4.14(2H, br. d, J=12.6Hz), 6.80(1H, d, J=7.2Hz) 6.95-7.50(7H, m), 7.76(4H, m), 8.20(2H, d, J=7.2Hz), 8.46(1H, d, J=7.2Hz)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
684	86	60-66	1.3-2.1(4H, m), 2.33(3H, s), 2.5-3.3(3H, m), 3.60(3H, s), 4.30(2H, br. d, J=12.6Hz), 6.48(1H, dd. J=4.0, 1.0Hz), 6.87(1H, d, J=7.2Hz) 7.0-7.5(9H, m), 7.82(2H, d, J=7.2Hz), 8.52(1H, d, J=7.2Hz)
692	100	56-60	0.3-1.9(5H, m), 2.33(3H, s), 2.44(2H, d, J=7.2Hz), 2.2-3.1(2H, m), 3.57(3H, s), 3.89(2H, br. d, J=12.6Hz), 6.64(1H, d, J=7.2Hz), 6.9-7.9(14H, m), 8.40(1H, d, J=7.2Hz)
700	96	136-138	2.5(2H, q, J=5.2Hz), 2.32(3H, s), 2.51(3H, s), 2.79(2H, t, J=5.2Hz), 3.58(3H, s), 4.04(2H, t, J=5.2Hz), 6.95(1H, d, J=7.2Hz), 7.11(2H, d, J=7.0Hz), 7.30(4H, s), 7.78(2H, d, J=7.2Hz), 8.58(1H, d, J=7.2Hz)
256	100	65-70	1.2-2.2(4H, m), 2.34(3H, s), 2.5-3.4(3H, m), 3.46(3H, s), 4.5(2H, br. d, J=12.6Hz), 6.9-7.6(12H, m), 7.78(2H, d, J=7.2Hz), 8.40(1H, d, J=7.2Hz)
288	100	80-85	1.2-2.0(4H, m), 2.32(3H, s), 2.5-3.3(3H, m), 3.55(3H, s), 4.47(2H, br. d, J=12.6Hz), 6.62(1H, d, J=7.2Hz) 6.9-7.9(18H, m), 8.33(1H, d, J=7.2Hz)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
138	66	121-123	0.88(3H, d, J=7Hz), 1.1-3.1(10H, m) 3.49(3H, s), 4.20(2H, m), 6.54(1H, d, J=7Hz), 7.12(2H, d, J=7Hz), 7.48(5H, m), 7.74(2H, d, J=7Hz), 8.26(1H, d, J=7Hz)
146	93	98-102	0.85(3H, t, J=7Hz), 1.0-3.2(15H, m) 3.47(3H, s), 4.26(2H, m), 6.58(1H, d, J=7Hz), 7.10(2H, d, J=7Hz), 7.48(5H, m), 7.72(2H, d, J=7Hz), 8.18(1H, d, J=7Hz)
147-1	44	98-100	0.85(6H, d, J=7Hz), 1.0-3.2(11H, m) 3.48(3H, s), 4.37(2H, m), 6.50(1H, d, J=7Hz), 7.10(2H, d, J=7Hz), 7.48(5H, m), 7.74(2H, d, J=7Hz), 8.24(1H, d, J=7Hz)
154	68	52-55	1.16(3H, d, J=7Hz), 1.60(5H, m), 2.34(3H, s), 2.5-3.3(2H, m), 3.50(3H, s), 4.18(1H, m), 4.52(1H, m), 6.50(1H, d, J=7Hz), 7.12(2H, d, J=7Hz), 7.48(5H, m), 7.76(2H, d, J=7Hz) 8.28(1H, d, J=7Hz)
171-3	81	128-129	1.3-2.2(4H, m), 2.33(3H, s), 2.40(3H, s), 2.5-3.4(3H, m), 3.52(3H, s), 4.58(2H, br. d, J=12.6Hz), 6.48(1H, d, J=7.2Hz), 7.0-7.9(13H, m), 8.28(1H, d, J=7.2Hz), 13.0-15.0(1H, m)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2004	64	167-169	0.89(6H, d, J=7Hz), 1.3-2.7(9H, m), 3.50(3H, s), 4.26(2H, m), 6.52(1H, d, J=7Hz), 7.12(2H, d, J=7Hz), 7.48(5H, m), 7.76(2H, d, J=7Hz), 8.28(1H, d, J=7Hz)
2012	83	186-187	1.4-2.2(4H, m), 2.33(3H, s), 2.44(3H, s), 2.5-3.4(3H, m), 3.55(3H, s), 4.65(2H, br. d, J=12.6Hz), 7.0-7.5(11H, m), 7.70(4H, m), 8.35(1H, d, J=7.2Hz)
2020	100	54-60	1.7-2.2(4H, m), 2.34(3H, s), 2.5-3.3(3H, m), 3.4-3.7(2H, m), 3.55(3H, s), 6.9-7.9(17H, m), 8.35(1H, m)
2028	100	60-70	2.4-3.1(4H, m), 2.35(3H, s), 2.5-3.2(3H, m), 3.50(3H, s), 4.24(2H, br. d, J=12.6Hz), 7.0-7.5(12H, m), 7.75(2H, m), 8.04(2H, m)
2036	100	54-58	1.4-2.1(8H, m), 2.32(6H, m), 2.2-3.3(6H, m), 3.55(3H, s), 4.50(4H, m), 6.95-7.8(23H, m), 9.1(2H, m)
2044	100	62-72	1.4-2.2(4H, m), 2.35(3H, s), 2.5-3.4(3H, m), 3.59(3H, s), 4.36(2H, br. d, J=12.6Hz), 6.48(1H, dd. J=3.6, 2.0Hz), 7.0-7.6(9H, m), 7.76(2H, d, J=7.2Hz), 7.97(1H, s), 8.15(1H, s), 10.92(1H, m)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2116	78	138-140	0.96(6H, s), 1.36(4H, m), 2.33(3H, s), 3.48(3H, s), 3.60(4H, m), 6.50(1H, d, J=7Hz), 7.12(2H, d, J=7Hz), 7.48(5H, m), 7.74(2H, d, J=7Hz), 8.24(1H, d, J=7Hz)
2124	61	145-147	0.91(3H, t, J=7Hz), 1.60(2H, m), 2.34(3H, s), 2.7-4.0(9H, m), 6.54(1H, d, J=7Hz), 7.0-7.6(12H, m) 7.76(2H, d, J=7Hz), 8.37(1H, d, J=7Hz)
2132	61	175-178	1.4-2.2(4H, m), 2.32(3H, s), 2.6-3.4(3H, m), 3.59(3H, s), 4.68(2H, br. d, J=12.6Hz), 6.63(1H, d, J=7.2Hz) 7.0-7.4(8H, m), 7.45-7.90(4H, m), 8.28(1H, d, J=7.2Hz), 12-14(1H, m)
2140	100	82-88	1.1-2.0(4H, m), 2.31(6H, s), 2.4-3.2(3H, m), 3.5(3H, s), 4.18(2H, br. d, J=12.6Hz), 6.81(1H, d, J=7.2Hz), 6.9-7.4(9H, m), 7.55-8.0(5H, m), 8.2-8.6(2H, m), 8.85(1H, d, J=5.2Hz), 9.10(1H, s), 9.62(2H, m)
2174	62	94-100	1.2-3.3(10H, m), 3.47(3H, s), 4.34(2H, m), 6.55(1H, d, J=7Hz), 6.9-7.9(14H, m), 8.08(1H, d, J=7Hz)
2182	78	>300	1.5-2.1(4H, m), 2.32(3H, s), 2.4-3.2(2H, m), 3.48(3H, s), 4.07-4.7(3H, m), 6.46(1H, d, J=7Hz) 6.72(2H, d, J=7Hz), 7.18(7H, m),

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2182	78	>300	7.48(2H, d, J=7Hz), 7.68(2H, d, J=7Hz), 7.88(1H, d, J=7Hz)
2188	60	151-156	1.4-3.2(10H, m), 3.41(3H, s), 4.40(2H, m), 6.50(1H, d, J=7Hz), 7.08(2H, d, J=7Hz), 7.42(5H, m), 7.66(2H, d, J=7Hz), 7.88(1H, d, J=7Hz)
2194	39	106-109	1.4-3.3(10H, m), 3.45(3H, s), 4.52(2H, m), 6.50(1H, d, J=7Hz), 7.0-8.1(19H, m)
2202	52	203-207	1.5-3.4(10H, m), 3.46(3H, s), 4.44(2H, m), 6.60(1H, d, J=7Hz), 7.10(2H, d, J=7Hz), 7.2-7.9(13H, m)
2210	100	62-66	1.3-2.2(10H, m), 2.31(3H, s), 2.5-3.6(7H, m), 3.25(3H, s), 4.72(2H, br. d, J=12.6Hz), 6.10(1H, d, J=7.2Hz), 7.0-7.4(7H, m), 7.75(2H, d, J=7.2Hz), 8.16(1H, d, J=7.2Hz)
2218	89	186-187	1.4-2.2(4H, m), 2.31(3H, s), 2.6-3.4(3H, m), 3.49(3H, s), 4.63(2H, br. d, J=12.6Hz), 6.76(1H, d, J=7.2Hz), 6.9-7.8(14H, m), 7.95(1H, d, J=7.2Hz), 10.20(1H, s)
2234	94	95-102	1.45-2.15(4H, m), 2.32(6H, s), 2.5-3.2(3H, m), 2.80(3H, s), 3.23(3H, s), 3.35(4H, m),

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2234	94	95-102	3.80(4H, m), 4.60(2H, br. d, J=12.6Hz), 6.62(1H, d, J=7.2Hz), 6.96-7.45(9H, m), 7.76(4H, d, J=7.2Hz), 8.23(1H, d, J=7.2Hz)
2242	76	116-117	1.40(3H, t, J=7.2Hz), 1.4-2.2(4H, m), 2.34(3H, s), 2.6-3.5(3H, m), 3.48(3H, s), 4.35(2H, q, J=7.2Hz), 4.76(2H, br. d, J=12.6Hz), 7.0-7.4(7H, m), 7.6(1H, d, J=7.2Hz), 7.78(2H, d, J=7.2Hz), 8.35(1H, d, J=7.2Hz), 14.0(1H, m)
2250	30	192-196	1.50-3.40(10H, m), 3.50(5H, s), 4.05(2H, s), 4.70(2H, m), 7.10(2H, d, J=7Hz), 7.23(10H, m), 7.48(1H, d, J=7Hz), 7.76(2H, d, J=7Hz), 8.35(1H, d, J=7Hz)
2260	45	166-173	0.85(3H, t, J=7Hz), 1.1-2.2(8H, m), 2.33(3H, s), 2.82(4H, m), 3.46(3H, s), 5.10(1H, m), 6.28(1H, d, J=7Hz), 7.10(2H, d, J=7Hz), 7.36(5H, m), 7.66(2H, d, J=7Hz), 7.96(1H, d, J=7Hz), 8.76(2H, m)
2270	50	168-169	1.52(4H, m), 2.30(3H, s), 2.4-3.2(3H, m), 3.42(3H, s), 4.40(2H, m), 6.46(1H, d, J=7Hz), 7.04(2H, d, J=7Hz), 7.36(15H, m), 7.66(2H, d, J=7Hz), 8.21(1H, d, J=7Hz)

to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2278	86	163-164	1.4-2.2(4H, m), 2.35(3H, s), 2.5-3.4(6H, m), 4.5-5.0(4H, m), 6.10(1H, d, J=7.2Hz), 7.0-7.5(12H, m), 7.80(2H, d, J=7.2Hz), 8.15(1H, m), 13.15(1H, m)
2286	90	204-207 (Decomp.)	1.4-2.15(4H, m), 2.33(3H, s), 2.5-3.3(3H, m), 3.48(3H, s), 4.70(2H, br. d, J=12.6Hz), 5.05(2H, s), 6.7-7.5(13H, m), 7.68(2H, m), 8.35(1H, m)
2294	100	48-52	1.4-2.15(4H, m), 2.32(3H, s), 2.6-3.2(3H, m), 3.0(6H, s), 3.26(3H, s), 4.73(2H, br. d, J=12.6Hz), 6.10(1H, d, J=7.2Hz), 7.0-7.4(7H, m), 7.76(2H, d, J=7.2Hz), 8.18(1H, d, J=7.2Hz)
2302	71	50-55	1.21(6H, t, J=7.2Hz), 1.5-2.2(4H, m), 2.32(3H, s), 2.5-3.7(10H, m), 4.70(2H, br. d, J=12.6Hz), 6.08(1H, m), 6.9-7.5(7H, m), 7.76(2H, d, J=7.2Hz), 8.18(1H, m), 13.33(1H, m)
2310	60	174-176	1.88(4H, m), 2.32(3H, s), 3.40(3H, m), 3.51(3H, s), 4.32(2H, m), 6.60(1H, d, J=7Hz), 7.10(2H, d, J=7Hz), 7.40(2H, d, J=7Hz), 7.50(5H, m), 7.74(2H, d, J=7Hz), 7.84(2H, d, J=7Hz), 8.24(1H, d, J=7Hz)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2318	67	80-85	1.4-2.1(4H, m), 2.6-3.4(3H, m), 3.92(3H, s), 7.0(1H, d, J=7Hz), 7.18(2H, d, J=7Hz), 7.1-7.8(10H, m) 7.78(2H, d, J=7Hz), 8.50(2H, d, J=7Hz)
2322	92	192-194	1.4-2.2(4H, m), 2.32(3H, s), 2.5-3.4(3H, m), 3.29(3H, s), 3.58(8H, m), 4.69(2H, br. d, J=12.6Hz), 6.20(1H, d, J=7.2Hz), 6.95-7.42(7H, m), 7.74(2H, d, J=7.2Hz), 8.23(1H, d, J=7.2Hz)
2330	78	160-162	1.4-2.2(4H, m), 2.32(3H, s), 2.6-3.6(3H, m), 3.69(3H, s), 4.79(2H, br. d, J=12.6Hz), 7.0-7.9(15H, m), 8.40(1H, d, J=7.2Hz)
154-2	86	191-193	1.4-2.2(4H, m), 2.32(3H, s), 2.5-3.4(3H, m), 3.44(3H, s), 3.47(3H, s), 4.4(2H, s), 4.70(2H, br. d, J=12.6Hz), 7.0-7.4(6H, m), 7.75(2H, d, J=7.2Hz), 8.40(1H, d, J=7.2Hz)
171-5	74	172-173	1.41(3H, t, J=7.2Hz), 1.4-2.2(4H, m), 2.32(3H, s), 2.5-3.4(3H, m), 3.52(3H, s), 4.05(2H, q, J=7.2Hz), 4.60(2H, br. d, J=12.6Hz), 6.40(1H, d, J=7.2Hz), 6.89(2H, d, J=7.2Hz), 7.0-7.5(7H, m), 7.56(2H, d, J=7.2Hz),

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, ppm)
171-5	74	172-173	7.75(2H, d, J=7.2Hz), 8.22(1H, d, J=7.2Hz)
298	70	217-218	1.6-2.2(4H, m), 2.35(3H, s), 2.7-3.5(3H, m), 4.90(2H, m), 7.22(8H, m), 7.88(6H, m), 8.75(1H, d, J=7Hz)
306	70	108-110	1.88(4H, m), 2.31(3H, s), 3.42(3H, m), 3.51(3H, s), 4.30(2H, m), 6.58(1H, d, J=7Hz), 7.10(2H, d, J=7Hz), 7.50(8H, m), 7.72(2H, d, J=7Hz), 7.88(2H, m), 8.24(1H, d, J=7Hz)
242	93	119-122	1.3-2.2(4H, m), 2.33(3H, s), 2.5-3.4(3H, m), 3.52(3H, s), 4.55(2H, br. d, J=12.6Hz), 6.59(1H, d, J=7.2Hz), 7.0-7.5(9H, m), 7.5-8.0(4H, m), 8.35(1H, d, J=7.2Hz)
2022-1	46	118-121	1.75-2.90(4H, m), 2.35(3H, s), 2.95-3.40(3H, m), 3.55(3H, s), 3.68(2H, br. d, J=12.6Hz), 6.9-8.0(16H, m), 8.70(1H, br. s)
2023-1	100	57-64	1.8-3.0(4H, m), 2.38(3H, s), 3.1-4.0(5H, m), 3,59(3H, s), 6.70-8.0(15H, m)
150	100	48-58	0.5-1.8(5H, m), 0.87(3H, d, J=5.2Hz), 2.35(3H, s), 2.4-3.2(2H, m), 3.4-4.5(2H, m), 6.22(1H, d, J=7.2Hz), 7.0-7.9(14H, m), 8.28(1H, d, J=7.2Hz)

- to be continued -

Table 4 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
171-9	88	137-139	1.2-2.2(4H, m), 2.32(3H, s), 2,5-3.4(3H, m), 3.51(3H, s), 4.44(2H, br. d, J=12.6Hz), 6.84(1H, d, J=7.2Hz), 6.9-7.9(14H, m), 8.40(1H, d, J=7.2Hz)
170-11	100	75-80	1.3-2.2(4H, m), 2.32(3H, s), 2.5-3.5(3H, m), 3.45(3H, s), 4.48(2H, br. d, J=12.6Hz), 6.95-7.5(11H, m), 7.72(2H, d, J=7.2Hz), 8.44(1H, d, J=7.2Hz)
170-2	88	147-148	1.4-2.1(4H, m), 2.33(3H, s), 2.5-3.5(3H, m), 3.55(3H, s), 4.72(2H, br. d, J=12.6Hz), 6.8-8.0(17H, m), 8.40(1H, d, J=7.2Hz)
171-7	95	70-76	1.3-2.1(4H, m), 2.32(3H, s), 2.36(3H, s), 2.5-3.3(3H, m), 3.44(3H, s), 4.56(2H, br. d, J=12.6Hz), 6.80(1H, d, J=7.2Hz), 9.0-9.6(11H, m), 7.73(2H, d, J=7.2Hz), 8.30(1H, d, J=7.2Hz)
171-13	97	154-158	1.2-2.1(4H, m), 2.3(3H, s), 2.5-3.3(3H, m), 3.48(3H, s), 4.4(2H, br. d, J=12.6Hz), 6.7(1H, d, J=7.2Hz), 7.0-7.9(12H, m), 8.39(1H, d, J=7.2Hz)

EXAMPLE 3

4-(N-methylbenzamino)-2-(4-phenylpiperidino)pyrimidine hydrochloride (coompound No. 170):-

A solution of 0.27 g (0.0027 mole) of concentrated hydrochloric acid in 2 ml of CH_3OH was slowly added to a solution of 1.0 g (0.0027 mole) of 4-(N-methylbenzamino)-2-(4-phenylpiperidino)pyrimidine in 10 ml of chloroform. After the addition, the mixture was concentrated under reduced pressure to give 1.1 g (yield 100 %) of the desired product.

Melting point: 80-84 °C.

^{1}H-NMR spectrum (deuterochloroform, δ ppm)

1.4-22(4H, m), 2.6-3.4(3H, m), 3.56(3H, s), 2.2(2H, m), 6.69(1H, d, J=7.2Hz), 7.0-7.7(10H, m), 8.1(1H, d, J=7.2Hz).

In the same way as above, the following compounds were produced, and their data are given in Table 5.

Table 5

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
662	46	241-243	10.9(1H, br), 8.03(1H, d, J=5Hz), 7.2-7.8(10H, m), 6.28(1H, d, J=5Hz), 4.63(2H, s), 3.50(3H, s), 3.0-3.4(1H, m), 1.48(6H, d, J=7Hz)
2052	86	96-99	12.9(2H, br), 8.03(1H, d, J=5Hz), 7.2-7.6(5H, m), 6.36(1H, d, J=5Hz), 4.5-4.8(2H, m), 3.56(3H, s), 1.1-3.3(17H, m)
2060	93	185-189	7.98(1H, d, J=7Hz), 7.3-7.7(5H, m), 6.64(1H, d, J=7Hz), 3.6-4.4(6H, m), 3.62(3H, s), 1.4-2.2(4H, m)
2070	93	77-80	8.03(1H, d, J=5Hz), 7.2-7.6(5H, m), 6.36(1H, d, J=5Hz), 4.0-4.7(2H, m), 3.63(3H, s), 1.0-4.0(12H, m)
2076	86	237-239	12.5(1H, br), 8.53(1H, d, J=5Hz), 8.12(9H, d, J=7Hz), 7.32(2H, d, J=7Hz), 6.43(1H, d, J=5Hz), 7.2-7.7(5H, m), 4.8-5.0(2H, m), 3.53(3H, s), 1.1-3.4(7H, m)
2084	90	60-63	12.3(1H, br), 8.70(1H, d, J=7Hz), 7.2-7.6(5H, m), 6.37(1H, d, J=7Hz), 4.0-4.8(2H, m), 2.63(3H, s), 0.8-3.5(14H, m)

- to be continued -

Table 5 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2092	86	183-186	8.06(1H, d, J=7Hz), 7.2-7.6(5H, m), 6.38(1H, d, J=7Hz), 3.60(3H, s), 3.10(3H, s), 1.8-4.0(10H, m)
2100	90	213-215	8.70(1H, d, J=5Hz), 7.3-7.6(5H, m), 6.48(1H, d, J=5Hz), 4.4-4.8(2H, m), 4,20(2H, q, J=7Hz), 3.58(3H, s), 1.32(3H, t, J=7Hz), 1.5-3.4(7H, m)
2108	93	89-91	10.5(1H, br), 8.07(1H, d, J=5Hz), 7.0-7.6(15H, m), 6.18(1H, d, J=5Hz), 4.68(4H, s), 3.44(3H, s)
2148	94	218-221	8.05(1H, d, J=7Hz), 7.2-7.5(5H, m), 6.40(1H, d, J=7Hz), 4.3-4.5(2H, m), 2.3-4.0(7H, m), 3.30(5.6H), 3.58(3H, s)
2156	89	57-60	14.0(1H, br), 8.04(1H, d, J=7Hz), 7.3-7.6(5H, m), 6.56(1H, d, J=7Hz), 3.50(3H, s), 4.0-4.8(2H, m), 1.0-2.4(14H, m)
2164	96	140-142	8.03(1H, d, J=5Hz), 7.2-7.6(5H, m), 6.40(1H, d, J=5Hz), 4.2-4.5(2H, m), 3.63(3H, s), 1.0-3.8(10H, m)

- to be continued -

Table 5 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
2226	86	187-189	7.9-8.1(3H, m), 7.2-7.7(8H, m), 6.66(1H, d, J=7Hz), 5.1-5.4(1H, m), 3.6-4.3(4H, m), 3.55(3H, s), 1.7-2.2(4H, m)
2342	94	135-138	12.0-12.8(1H, br), 8.03(1H, d, J=7Hz), 7.2-7.6(5H, m), 6.50(1H, d, J=7Hz), 3.53(3H, s), 1.0-3.7(13H, m)
2350	88	153-157	12.8(1H, br), 8.03(1H, d, J=7Hz), 7.2-7.9(10H, m), 6.60(1H, d, J=7Hz), 4.3-4.6(2H, m), 3.50(3H, s), 1.5-4.0(7H, m)
307-1	94	259-261	8.07(1H, d, J=7Hz), 7.2-7.6(5H, m), 6.38(1H, d, J=7Hz), 4.2-4.4(2H, m), 3.50(3H, s), 1.4-4.0(10H, m)

The following compounds were obtained by the same method as in Example 3 except that sulfuric acid, phosphoric acid, etc. were used instead of hydrochloric acid.

Table 6

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
165	84	151-154	1.0-2.0(4H, m),2.5-3.2(3H, m), 3.45(3H, s), 4.24(2H, br. d, J=12.6Hz), 6.67(1H, d, J=7.2Hz), 6.73(1H, d, J=7.2Hz), 7.0-7.6(10H, m), 8.15(1H, d, J=7.2Hz)
166	67	108-113	1.2-2.0(4H, m), 2.5-3.0(3H, m), 3.51(3H, s), 4.58(2H, br. d, J=12.6Hz), 6.15(1H, d, J=5.4Hz), 7.0-7.55(10H, m), 8.02(1H, d, J=5.4Hz), 11.0(1H, m)
167	37	94-96	1.3-2.2(4H, m), 2.6-3.2(3H, m), 3.52(3H, s), 4.54(2H, br. d, J=12.6Hz), 6.32(2H, s), 6.49(1H, d, J=7.2Hz), 7.0-7.7(10H, m), 8.15(1H, d, J=7.2Hz), 8.93(2H, br. s)
169	32	132-136	1.3-2.2(4H, m), 2.55-3.3(3H, m), 3.49(3H, s), 4.49(2H, br. d, J=12-6Hz), 6.58(1H, d, J=7.2Hz), 6.8-8.5(19H, m)
171	45	108-112	1.0-1.9(4H, m), 2.4-2.9(6H, m), 3.0-3.6(3H, m), 3.40(3H, s), 4.36(2H, br. d, J=12.6Hz), 6.42(1H, d, J=5.4Hz), 7.0-7.4(5H, m), 7.35(5H, s), 8.15(1H, d, J=5.4Hz), 12-13(2H, m)

- to be continued -

Table 6 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
171-1	49	133-135	1.0-1.8(4H, m), 2.4-2.9(3H, m), 3.0-3.5(3H, m), 3.40(3H, s), 4.30(2H, s), 4.38(2H, br. d, J=12.6Hz), 6.42(1H, d, J=5.4Hz), 7.0-7.4(5H, m), 7.35(5H, s), 8.15(1H, d, J=5.4Hz), 12-13(1H, m)
171-1-1	90	124-127	1.2-2.0(4H, m), 2.5-3.0(3H, m), 3.48(3H, s), 4.55(2H, br. d, J=12.6Hz), 6.17(1H, d, J=5.4Hz), 6.69(2H, s), 6.9-7.5(10H, m), 8.02(1H, d, J=5.4Hz)

EXAMPLE 4

Production of 2-isopropylamino-4-methyl-5-methoxycarbonylpyrimidine (compound No. 800):-

18.2 g (0.12 mole) of 1-amidinoisopropylamine sulfate was added to a solution of 13.0 g (0.12 mole) of potassium t-butoxide in 200 ml of methanol, and the mixture was stirred at room temperature for 30 minutes. Then, 18.5 g (0.12 mole) of ethyl 2-methoxymethyleneacetoacetate was added at 0 °C over 30 minutes, and the mixture was stirred for 3 hours. The solvent was evaporated, and the residue was extracted with ether and purified by silica gel column chromatography to give 10.6 g (yield 44 %) of the desired product as a yellow solid.

Melting point: 118-119 °C.

^{1}H-NMR spectrum (deuterochloroform, δ ppm)

1.26(6H, d, J = 7Hz), 2.66(3H, s), 3.87(3H, s), 4.25(1H, sex, J = 7Hz), 5.40(1H, br. s), 8.80(1H, s).

EXAMLPLE 5

Production of 2-piperidino-4-methoxymethyl-5-methoxycarbonylpyrimidine (compound No. 820):-

Sodium hydride (0.19 g; 7.8 mmoles) was added to 50 ml of methanol, and 2.1 g (7.8 mmoles) of 2-piperidino-4-chloromethyl-5-methoxycarbonylpyrimidine was added at room temperature. The mixture was stirred for 3 hours. After the solvent was evaporated, water was added to the residue and the mixture was extracted with ethyl acetate. The ethyl acetate layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography to give 0.90 g (yield 44 %) of the desired product as a white solid.

Melting point: 89-92 °C.
^{1}H-NMR spectrum (deuterochloroform, δ ppm):
1.70(6H, m), 3.54(3H, s), 3.86(3H, s), 3.92(4H, m), 4.83(2H, s), 8.82(1H, s).
In the same way as above, the following compounds were obtained.

Table 7

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δppm)
808	53	Oil	1.35(3H, t, J=7Hz), 1.66(6H, m), 2.44(3H, s), 3.90(2H, s), 3.92(4H, m), 4.30(2H, q, J=7Hz), 8.80(1H, s)
816	35	Oil	1.40(3H, t, J=7Hz), 1.70(6H, m), 2.21(3H, s), 3.92(4H, m), 4.06(2H, s), 4.36(2H, q, J=7Hz), 8.91(1H, s)
824	90	Oil	1.22(6H, d, J=8Hz), 1.33(3H, t, J=8Hz), 2.36(6H, s), 3.84(2H, s), 5.5(1H, br,s), 8.78(1H, s)

EXAMPLE 6

Production of 2-isopropylamino-4-methyl-5-methoxycarbonylpyrimidine maleate (compound No. 804):-

2.48 g (11.9 mmoles) of 2-isopropylamino-4-methyl-5-methoxycarbonylpyrimidine and 1.38 g (11.9 mmoles) of maleic acid were dissolved in a mixture of 20 ml of ethanol and 20 ml of chloroform, and the solution was stirred for 3 hours. The solvents were evaporated, and ether was added for crystallization at 0 °C. The desired product was obtained in an amount of 3.21 g (yield 83 %) as pale yellow crystals.
Melting point: 75-79 °C.
^{1}H-NMR spectrum (deuterochloroform, δ ppm):
1.33(6H, d, J=7Hz), 2.85(3H, s), 3.95(3H, s), 4.36(1H, sex, J=7Hz), 6.40(2H, s), 9.08(1H, br, s).
In the same way as above, the following compounds were produced.

Table 8

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
812	74	115.5-118.5	1.40(3H, t, J=7Hz), 1.68(6H, m), 3.08(3H, s), 3.92(4H, m), 4.34(2H, q, J=7Hz), 4.72(2H, s), 6.32(2H, s), 8.90(1H, s)
828	67	111-121	1.30(6H, d, J=8Hz), 1.40(3H, t, J=8Hz), 3.07(6H, s), 4.34(2H, q, J=8Hz), 4.66(2H, s), 6.32(2H, s), 8.92(1H, s)

EXAMPLE 7

Production of 2-(4-diphenylmethylpiperazino)-5,6-dihydro-7-methyl-6-oxo(7H)pyrrolo[2,3-d]pyrimidine (compound No. 3124):-

1.9 g (7.5 mmoles) of 1-diphenylmethylpiperazine and 1.7 g (7.5 mmoles) of ethyl (2-methylthio-4-hydroxypyrimidin-5-yl)acetate were added to 60 ml of n-amyl alcohol, and the mixture was stirred at 170 °C for 20 hours. The solvent was then evaporated under reduced pressure. Ten milliliters of phosphorus oxychloride was added to the residue, and reacted at 100 °C for 2 hours. After the reaction, the mixture was gradually added to an aqueous solution of potassium carbonate, and extracted with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue, 15 ml of ethanol and a 40 % methanol solution of methylamine was put in a pressure vessel, and reacted at 140 °C for 10 hours. Then, the solvent was evaporated, and the residue was purified by silica gel column chromatography to give 0.9 g (yield 30 %) of the desired product.
Melting point: 75-80 °C.
^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm):
2.43(4H, m), 3.13(3H, s), 3.37(2H, s), 3.80(4H, m), 4.23(1H, s), 7.08-7.52(10H, m), 7.82(1H, s).

The following compounds were produced in the same way as above, and their data are shown in Table 9.

Table 9

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
3100	78	210-213	2.47(4H, m), 3.17(3H, s), 3.39(2H, s), 3.50(2H, s), 3.82(4H, m), 7.28(4H, m), 7.88(1H, s)
3108	56	82-86	0.74(3H, d, J=7Hz), 1.02(3H, d, J=7Hz), 2.38(4H, m), 3.13(3H, s), 3.35(2H, s), 3.74(4H, m), 4.10(1H, m), 7.20(5H, m), 7.80(1H, s)
3132	38	80-85	2.42(4H, m), 3.15(3H, s), 3.38(2H, s), 3.81(4H, m), 4.24(1H, s), 6.8-7.5(9H, m), 7.85(1H, s)
3140	54	105-110	2.43(4H, m), 3.15(3H, s), 3.39(2H, s), 3.82(4H, m), 4.24(1H, s), 7.32(9H, m), 7.88(1H, s)
3148	35	-	2.29(3H, s), 2.43(4H, m), 3.14(3H, s), 3.38(2H, s), 3.80(4H, m), 4.21(1H, s), 6.9-7.5(9H, m), 7.84(1H, s)
3172	26	-	2.41(4H, m), 3.14(3H, s), 3.36(2H, s), 3.80(4H, m), 4.22(1H, s), 7.28(8H, m), 7.84(1H, s)
3180	12	91-94	2.40(4H, m), 3.14(3H, s), 3.37(2H, s), 3.80(4H, m), 4.23(1H, s), 6.8-7.4(8H, m), 7.83(1H, s)
3188	44	170-175	2.50(4H, m), 3.16(3H, s), 3.40(2H, s), 3.84(4H, m), 4.44(1H, s), 7.1-7.6(8H, m), 7.84(1H, s), 8.49(1H, m)

- to be continued -

Table 9 (continued)

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
3196	51	179-181	2.66(4H, m), 3.12(3H, s), 3.36(2H, s), 3.76(4H, m), 4.88(1H, s), 7.28(4H, m), 7.70(4H, m), 7.84(1H, s)
3300	49	263-267 (decomp.)	2.36(4H, m), 3.13(3H, s), 3.36(2H, s), 3.92(4H, m), 7.1-7.6(15H, m), 7.82(1H, s)
3400	40		2.78(3H, s), 3.18(3H, s), 3.26(4H, m), 3.40(2H, s), 3.94(4H, m), 7.87(1H, s)
3408	68		1.1-2.0(12H, m), 3.18(3H, s), 3.32(4H, m), 4.20(2H, m), 7.84(1H, s)
3416	61		1.2-2.4(12H, m), 3.18(3H, s), 3.3-3.8(4H, m), 7.86(1H, s)

EXAMPLE 8

Production of 2-(4-diphenylmethylpiperazino)-5,6-dihydro-7-methyl-6-oxo(7H)pyrrolo[2,3-d]pyrimidine hydrochloride (compound No. 3128):-

Concentrated hydrochloric acid (0.23 g; 2.2 mmoles) was added to an ethanol/methylene chloride solution of 2-(4-diphenylmethylpiperazino)-5,6-dihydro-7-methyl-6-oxo(7H)pyrrolo[2,3-d]pyrimidine, and the solution was stirred at room temperature for 1 hour. The solvent was then evaporated under reduced pressure. The residue was washed with ether to give 0.88 g (yield 90 %).

Melting point: 217-222 °C.

^{1}H-NMR spectrum ($CDCl_3$, δ ppm):

3.18(3H, s), 3.20(4H, m), 3.52(2H, s), 4.40(4H, m), 5.20(1H, s), 7.2-7.9 (1H, m).

In the same way as above, the following compounds were produced, and their data are shown in Table 10.

Table 10

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
3104	82	>300	($CDCl_3$-CD_3OD) 3.20(3H, s), 3.30(4H, m), 3.48(2H, s), 4.32(2H, s), 4.54(4H, m), 7.52(4H, m), 7.93(1H, s)
3136	80	238-243 (decomp.)	($CDCl_3$-CD_3OD) 3.20(3H, s), 3.24(4H, m), 3.50(2H, s), 3.8-4.6(4H, m), 5.10(1H, s), 7.0-8.0(10H, m)
3144	93	238-245 (decomp.)	3.20(3H, s), 3.29(4H, m), 3.57(2H, s), 4.58(4H, m), 5.26(1H, s), 7.40(5H, m), 7.90(5H, m)
3200	73	244-245 (decomp.)	3.12(3H, s), 3.14(4H, m), 3.40(2H, s), 4.56(4H, m), 5.45(1H, s), 7.17-8.27(9H, m)
3412	70	250-252 (decomp.)	1.2-2.2(12H, m), 3.26(3H, s), 3.52(4H, m), 4.50(2H, m), 8.00(1H, s)
3420	70	256-257 (decomp.)	1.2-2.5(12H, m), 3.25(3H, s), 3.3-4.2(4H, m), 7.99(1H, s)

EXAMPLE 9

Production of 2-(4-(α-(4-methylphenyl)benzyl)piperazino)-5,6-dihydro-7-methyl-6-oxo(7H)pyrrolo[2,3-d]-pyrimidine p-toluenesulfonate (compound No. 3152):-

An ethyl acetate/methanol solution of 0.13 g (0.75 mmole) of p-toluenesulfonic acid was added to an ethyl acetate/methanol solution of 0.31 g (0.75 mmole) of 2-(4-(α-(4-methylphenyl)benzyl)piperazino)-5,6-dihydro-7-methyl-6-oxo(7H)pyrrolo[2,3-d]pyrimidine, and the mixture was stirred at room temperature for 1 hour. The solvents were then evaporated under reduced pressure, and the residue was washed with hexane

to give 0.36 g (yield 81 %) of the desired compound.
Melting point: 150-155 °C.
^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm):
2.28(3H, s), 2.34(3H, s), 3.00(4H, m), 3.11(3H, s), 3.39(2H, s), 4.14(4H, m), 4.73 (1H, s), 7.0-7.8(13H, m), 7.93(1H, s).

In the same way as abvove, the following compounds were produced, and their data are shown in Table 11.

Table 11

Compound No.	Yield (%)	Melting point (°C)	^{1}H-NMR spectrum ($CDCl_3$ solution, δ ppm)
3112	92	-	0.86(3H, d, J=7Hz), 1.16(3H, d, J=7Hz), 2.35(3H, s), 3.12(7H, m), 3.39(2H, s), 4.20(5H, m), 7.14(2H, d, J=7Hz), 7.35(5H, m), 7.76(2H, d, J=7Hz), 7.87(1H, s)
3176	90	145-150	2.34(3H, s), 2.83(4H, m), 3.13(3H, s), 3.43(2H, s), 4.06(4H, m), 4.72(1H, s), 7.0-7.5(10H, m), 7.66(2H, d, J=7Hz), 8.03(1H, s)
3184	91	124-130	2.34(3H, s), 2.74(4H, m), 3.14(3H, s), 3.43(2H, s), 4.04(4H, m), 4.56(1H, s), 6.8-7.8(12H, m), 8.01(1H, s)
3192	100	135-140	2.35(3H, s), 3.0-3.4(4H, m), 3.16(3H, s), 3.44(2H, s), 4.18(4H, m), 5.34(1H, s), 7.0-7.8(8H, m), 7.11(2H, d, J=7Hz), 7.74(2H, d, J=7Hz), 7.96(1H, s), 8.60(1H, m)
3404	70	220-223 (decomp.)	($CDCl_3$-CD_3OD) 2.38(3H, s), 2.86(3H, s), 3.27(3H, s), 3.38(4H, m), 3.60(2H, s), 4.03(4H, m), 7.16(2H, d, J=7Hz), 7.64(2H, d, J=7Hz), 8.02(1H, s)

EXAMPLE 1B

Tablets each containing 10 mg of an active ingredient were prepared by the following procedure.

	Per tablet
Active ingredient	10 mg
Corn starch	55 mg
Crystalline cellulose	35 mg
Polyvinyl pyrrolidone (as 10% aqueous solution)	5 mg
Carboxymethyl cellulose calcium	10 mg
Magnesium stearate	4 mg
Talc	1 mg
Total	120 mg

The active ingredient, corn starch and crystalline cellulose were passed through an 80-mesh sieve and thoroughly mixed. The mixed powder was granulated together with the polyvinyl pyrrolidone solution, and passed through an 18-mesh sieve. The resulting granules were dried at 50 to 60 °C and again passed through an 18-mesh sieve to adjust their sizes. The carboxymethyl cellulose calcium, magnesium stearate and talc, which had been passed through an 80-mesh sieve, were added to the granules. They were mixed and tableted by a tableting machine to produce tablets each having a weight of 120 mg.

EXAMPLE 2B

Tablets each containing 200 mg of an active ingredient were produced by the following procedure.

	Per tablet
Active ingredient	200 mg
Corn starch	50 mg
Crystalline cellulose	42 mg
Silicic anhydride	7 mg
Magnesium stearate	1 mg
Total	300 mg

The above components were passed through an 80-mesh sieve and thoroughly mixed. The resulting mixed powder was compression-molded to produce tablets each having a weight of 300 mg.

EXAMPLE 3B

Capsules each containing 100 mg of an active ingredient were produced by the following procedure.

	Per capsule
Acive ingredient	100 mg
Corn starch	40 mg
Lactose	5 mg
Magnesium stearate	5 mg
Total	150 mg

The above components were mixed, passed through an 80-mesh sieve, and thoroughly mixed. The resulting mixed powder was filled into capsules in an amount of 150 mg for each.

EXAMPLE 4B

Injectable preparations in vials each containing 5 mg of an active ingredient were produced by the following procedure.

	Per vial
Active ingredient	5 mg
Mannitol	50 mg

Just prior to use, these compounds were dissolved in 1 ml of distilled water for injection, and administered.

EXAMPLE 5B

Injectable preparations in ampoules each containing 50 mg of an active ingredients were produced in accordance with the following recipe.

	Per ampoule
Active ingredient	50 mg
Sodium chloride	18 mg
Distilled water for injection	proper amount
Total	2 ml

EXAMPLE 6B

An adhesive patch containing 17.5 mg of an active ingredient was produced by the following procedure.

Ten parts of poly(ammonium acrylate) was dissolved in 60 parts of water. Two parts of glycerin diglycidyl ether was dissolved under heat in 10 parts of water. Furthermore, 10 parts of polyethylene glycol (grade 400), 10 parts of water and 1 part of an active ingredient were stirred to form a solution. While the aqueous solution of poly(ammonium acrylate) was stirred, the aqueous solution of glycerin diglycidiyl ether and the solution containing the active ingredient, polyethylene glycol and water were added and mixed. The resulting solution for hydrogel was coated on a pliable plastic film so that the rate of the active ingredent was 0.5 mg per cm^2. The surface was covered with releasing paper and cut to a size of 35 cm^2 to form an adhesive patch.

EXAMPLE 7B

An adhesive patch containing 10 mg of an active ingredient was produced by the following procedure.

An aqueous sol is prepared from 100 parts of poly(sodium acrylate), 100 parts of glycerin, 150 parts of water, 0.2 part of triepoxypropyl isocyanurate, 100 parts of ethanol, 25 parts of isopropyl myristate, 25 parts

of propylene glycol and 15 parts of the active ingredient. The sol was then coated to a thickness of 100 micrometers on the non-woven fabric surface of a composite film composed of a rayon non-woven fabric and a polyethylene film to form an adhesive layer containing the drug. The amount of the release aids (isopropyl myristate and propylene glycol) contained in this layer was about 30 % by weight. The adhesive layer was then crosslinked at 25 °C for 24 hours, and a releasing film was bonded to the adhesive layer surface. The entire film was then cut into pieces each having an area of 35 cm^2.

The biological activities in vitro of the compounds of formula (1), (2) or (3) on cells of the nervous system were tested. The cells tested were mouse neuroblastoma cell line neuro-2a (Dainippon Pharmaceutical Co., Ltd.), NS-20Y, etc. which have been established as the cells of the nervous system. The above nerve cells were grown in an incubator at 37 °C in the presence of 5 % carbon dioxide gas exponentially, and then cultivated for a certain period of time together with the compounds of the invention. The results demonstrate that the compounds of the invention have nerve cell growth promoting activity and neurite formation and sprouting promoting activity which are markedly higher with a significance than a control, and are equal to, or higher than, isaxonine as a control drug (the compound described in Japanese Patent Publication No. 28548/1984).

The biological activities of the compounds of the invention on rat PC-12 pheochromocytoma cell line were also tested. When NGF is added to PC-12 cells, the neurites sprout. It was shown that when the compound of this invention is added at this time, the binding of NGF to the PC-12 cells and the up-take of NGF into the cells increased, and that the sprouting of the neurites also increased.

When the effect of the compounds of this invention on the binding of NGF to rabbit superior cervical ganglion was examined, they were found to promote the NGF binding.

Rats having crushed sciatic nerves were prepared as a model of peripheral nervous disorder, and the effects of the compounds of this invention on it were tested. It was made clear that the compounds of the present invention have an effect of promoting recovery of the interdigit distance and the weight of the soleus muscle to normal values.

Rat and mouse models of central nervous disorders were prepared, and the pharmacological effects of the compounds of this invention were tested. Specifically, nigral dopamine cells of the rat brain were chemically destroyed by injecting a very small amount of 6-hydroxydopamine to induce motor imbalance. Two weeks later, dopamine cells of fetal brain were transplanted into the lesioned side of the caudate nucleus of the rat brain and an attempt was made to improve the motor trouble. Specifically, beginning on the day of transplantation, the compound of the invention was intraperitoneally administered every day over 2 weeks, and the activity of the compounds of the invention on the improvement of the motor imbalance and the growth of the transplanted cells were examined. It was found that the compounds of the invention have a promoting effect on the improvement of the motor trouble.

Rats and mice having a nerve trouble by mercury poisoning were prepared and the activity of the compounds of the invention was tested. The compounds of the invention were found to have a promoting effect on the improvement of the condition and recovery to a normal condition, a curative effect on chemical-induced disorders and an effect of improving and recovering learning and memory.

Thus, it has been made clear that the compounds of this invention are useful as agents for improving or curing various neurological diseases of mammals, such as troubles in peripheral and central nerves, and also as agents for improving learning and memory.

Various types of neuropathy including, for example, various peripheral nerve disorders accompanied by motorgenic, seonsory or objective flex retardation, and alcohol-induced or drug-induced, diabetic and meta bolic, or idiopathic peripheral nerve disorders, including traumatic, inflammatory or immunological nerve root lesions may be cited as such neurological diseases. More specific examples include facial palsy, sciatic nerve paralysis, spinal muscular atrophy, muscular dystrophy, myasthenia gravis, multiple sclerosis, amyotrophic lateral sclerosis, acute disseminated cerebromyelitis, Guillan-Barre syndrome, postvaccinal encephalomyelitis, SMON disease, dementia, Alzheimer syndrome, a condition after cranial injury, cerebral ischemia, sequela of cerebral infarction or cerebral hemorrhage, cerebrospinal injury and rheumatism. These examples are not limitative.

By a toxicity test, the compounds of this invention were found to have only weak toxicity and side effects, and be used as safe and useful medicines.

EXPERIMENTAL EXAMPLE 1

The effects of the compounds of this invention on neuroblastoma cells were examined by the following

method.

Mouse neuro 2a cells in the logarithmic growth period in the Dulbecco's modified Eagle's medium [DMEM, containing 100 units/ml of penicillin G sodium and 100 micrograms/ml of streptomycin sulfate] containing 10 % of FCS were seeded in a 48-well plate so that the number of cells was 1,000 cells/well, and cultured for one day in 0.25 ml of the culture fluid in each well in an incubator containing 5 % of carbon dioxide gas in air at 37 °C. Then, a 4 % aqueous glutaraldehyde solution in the same amount as a medium (0.25 ml) was added, and the culture fluid was left to stand at room temperature for 2 hours to fix the cells. After washing with water, a 0.05 % aqueous solution of methylene blue was added to stain the cells. Under a microscope, the number of cells containing outgrown neurites (cells having at least one neurite with a length of at least two times as large as the long diameter of the cell) was counted visually, and the proportion of these cells in the entire cells was calculated. The well was observed over 5 or more visual fields (at least 2 % of the entire surface area of the well) continuous to the left and right from a mark put at the center of the well, and more than 200 cells was counted. One drug compound was used in 6 different concentrations at most, and three runs were conducted for each concentrations. The results were expressed as a mean ±S.D., and the results are shown in Table 12.

Mouse neuroblastoma cells NS-20Y were similarly cultured in a dish coated with polyornithine, and the effects of the compounds were examined. The results obtained after 24 hours and 48 hours from the start of culturing are shown in Table 13.

Table 12

Action on neuro - 2a

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
1	1034	3.9±2.8(0.03mM), 7.6±2.1(0.1mM), 11.3±1.6(0.3mM)
	312	4.5±0.4(0.03mM), 9.7±0.9(0.1mM)
	isaxonine	26.7±7.7(10mM)
	control	1.8±0.8
2	128	9.9±0.6(0.3mM), 9.1±0.7(0.5mM), 19.8±2.8(1mM), 14.3±2.4(2mM)
	208	7.2±2.3(0.5mM), 10.6±1.5(1mM), 11.1±1.2(2mM), 8.0±4.0(3mM)
	168	23.8±2(0.05mM), 35.7±0.8(0.1mM), 24.4±6.9(0.2mM), 14.6±4.3(0.3mM)
	isaxonine	28.5±5.4(10mM)
	control	1.4±0.2
3	384	10.4±2.5(0.3mM), 10.8±7.2(1mM)
	392	14.6±6.0(0.1mM), 30.9±5.7(0.3mM), 23.8±4.2(1mM), 11.1±9.7(3mM)
	700	5.9±1.4(0.1mM), 6.4±1.4(0.3mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
3	isaxonine	30.8±2.9(10mM)
	control	3.2±1.6
4	416	13.2±1.3(0.1mM), 10.8±1.5(0.3mM)
	320	7.2±0.2(0.1mM0, 8.5±1.1(0.3mM)
	328	6.6±0.5(0.01mM), 10.2±8.2(0.03mM), 28.0±6.8(0.1mM), 10.6±3.4(0.3mM)
	400	11.4±4.3(0.3mM), 16.0±2.7(1mM)
	isaxonine	30.7±5.9(10mM)
	control	2.9±1.9
5	136	11.6±6.3(0.1mM), 12.1±2.9(0.3mM)
	628	10.2±1.3(0.03mM), 13.4±3.2(0.1mM), 12.6±3.2(0.3mM), 10.0±3.9(1mM)
	144	13.7±7.8(0.1mM), 33.8±8.6(0.3mM)
	408	9.1±1.8(0.1mM), 9.6±3.9(0.3mM)
	isaxonine	23.8±4.0(10mM)
	control	1.8±0.8

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
6	264	5.2±3.1(0.1mM), 8.7±1.6(0.3mM), 15.2±3.2(1mM), 7.2±1.8(3mM)
	424	4.5±1.4(0.03mM), 7.6±1.3(0.1mM)
	isaxonine	27.3±4.4(10mM)
	control	2.1±0.5
7	360	6.5±0.7(0.03mM), 10.0±0.7(0.1mM)
	272	4.8±1.3(0.03mM), 30.9±2.8(0.1mM), 15.9±0.5(0.3mM), 17.0±4.3(1mM)
	676	4.2±2.1(1.0mM), 6.0±1.1(0.3mM)
	isaxonine	27.3±4.4(10mM)
	control	1.8±0.5
8	240	19.8±5.7(0.03mM), 38.7±4.5(0.1mM), 33.2±0.9(0.3mM), 30.9±5.9(1mM)
	296	44.4±5.5(0.1mM), 22.4±3.0(0.3mM)
	170	33.5±2.4(0.1mM), 31.0±4.6(0.3mM)
	224	4.6±1.7(0.03mM), 5.5±1.5(0.1mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
8	432	2.9±1.0(0.1mM), 3.6±1.7(0.3mM)
	604	18.7±4.1(0.1mM), 24.6±2.9(0.3mM)
	612	13.8±1.5(0.01mM), 19.1±3.0(0.03mM), 19.4±3.9(0.1mM), 22.4±2.4(0.3mM)
	isaxonine	21.1±0.6(10mM)
	control	1.7±1.3
9	636	12.1±3.4(0.03mM), 8.9±5.2(0.1mM)
	176	5.3±1.9(0.03mM), 3.2±3.1(0.1mM)
	184	18.8±4.7(0.1mM), 16.0±2.4(0.3mM)
	644	26.1±7.3(0.03mM), 14.7±7.3(0.1mM)
	620	4.7±0.4(0.01mM), 4.0±1.3(0.03mM)
	652	6.1±0.6(0.03mM), 12.5±2.8(0.1mM)
	152	6.2±2.3(0.03mM), 33.8±4.7(0.1mM)
	isaxonine	27.5±0.8(10mM)
	control	1.4±0.7

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
10	376	13.6±1.2(0.03mM), 14.7±1.5(0.1mM), 17.2±1.4(0.3mM), 16.4±3.0(1mM)
	200	4.2±1.6(0.01mM), 7.6±1.6(0.03mM)
	192	12.1±1.5(0.3mM), 14.6±1.0(1mM)
	isaxonine	27.8±2.5(10mM)
	control	3.0±0.8
11	660	13.5±1.3(0.03mM), 9.1±3.7(0.1mM)
	304	38.1±1.6(0.1mM), 15.3±6.3(0.3mM)
	isaxonine	30.7±3.8(10mM)
	control	2.6±0.5
12	692	5.8±0.9(0.03mM), 11.1±2.9(0.1mM)
	160	11.3±6.3(0.1mM), 6.7±4.3(0.3mM)
	isaxonine	23.9±1.8(10mM)
	control	1.5±1.5
13	668	5.6±0.8(0.01mM), 4.8±0.4(0.03mM),

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
13	668	5.2±0.7(0.1mM), 4.1±2.5(0.3mM)
	684	3.8±0.5(0.01mM), 5.8±2.0(0.03mM), 16.4±2.8(0.1mM)
	280	4.5±1.2(0.03mM), 17.2±1.3(0.1mM), 13.4±3.5(0.3mM), 17.4±2.6(1mM)
	isaxonine	15.8±2.2(3mM)
	control	2.9±1.0
14	368	3.5±0.5(0.03mM), 9.0±1.8(0.1mM)
	344	3.6±0.7(0.01mM), 4.0±1.7(0.03mM), 4.7±1.8(0.1mM), 4.5±2.1(0.3mM)
	isaxonine	16.8±3.4(3mM)
	control	2.6±0.6
15	336	5.8±2.4(0.1mM), 6.3±2.8(0.3mM)
	120	4.9±1.0(0.1mM), 7.5±4.1(0.3mM)
	232	3.9±1.8(0.03mM), 18.7±5.2(0.1mM)
	248	4.3±0.4(0.03mM), 25.4±3.0(0.1mM), 21.5±5.7(0.3mM), 17.4±4.5(1mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
15	isaxonine	19.4±3.1(3mM)
	control	3.2±1.2
16	812	3.5±0.5(0.1mM), 3.4±0.5(0.3mM)
	816	4.7±2.1(0.03mM), 4.0±0.3(0.1mM)
	820	8.4±1.1(1mM), 8.8±2.3(3mM)
	800	11.4±1.2(0.3mM), 25.7±1.9(1mM), 22.3±0.7(3mM), 16.9±0.8(10mM)
	828	7.3±1.6(0.3mM), 6.1±2.0(1mM)
	isaxonine	27.0±3.8(10mM)
	control	2.3±0.4
17	1014	4.7±0.7(0.1mM), 7.6±1.5(0.3mM)
	1122	4.2±2.1(0.01mM), 10.2±3.8(0.03mM)
	1026	3.5±0.5(0.03mM), 5.6±2.2(0.1mM)
	1130	1.8±0.5(0.03mM), 2.0±0.3(0.1mM)
	1038	2.2±0.4(0.03mM), 2.9±0.3(0.1mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
17	isaxonine	27.4±2.4(10mM)
	control	1.8±1.3
18	112	4.8±0.1(0.03mM), 18.6±5.2(0.1mM), 2.6±0.6(0.3mM), 7.6±4.9(1mM)
	216	3.7±0.4(0.01mM), 6.3±2.4(0.03mM), 26.6±5.6(0.1mM)
	isaxonine	23.3±2.9(10mM)
	control	2.3±0.6
19	104	2.5±0.8(0.03mM), 4.1±1.5(0.1mM), 7.7±3.8(0.3mM), 3.6±1.4(1mM)
	352	3.2±1.9(0.1mM), 9.9±1.6(0.3mM)
	isaxonine	22.6±0.5(10mM)
	control	1.8±1.4
20	288	1.4±0.1(0.03mM), 3.3±0.9(0.1mM), 3.8±1.9(0.3mM), 5.1±2.7(1mM)
	256	4.5±0.6(0.03mM), 17.9±6.3(0.1mM), 21.6±4.9(0.3mM), 16.6±2.5(1mM)
	isaxonine	19.4±3.1(10mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
20	control	2.2±1.0
21	1086	1.9±1.8(0.03mM), 3.1±1.3(0.1mM), 8.7±0.8(0.3mM), 17.4±1.1(1mM)
	1110	3.4±1.1(0.01mM), 4.4±0.3(0.03mM), 6.3±4.4(0.1mM), 16.5±2.1(0.3mM)
	isaxonine	30.2±3.5(10mM)
	control	2.6±1.0
22	1090	3.7±1.0(0.01mM), 5.7±0.6(0.03mM), 12.2±2.5(0.1mM), 10.3±0.9(0.3mM)
	1158	9.9±1.4(0.03mM), 18.4±3.0(0.1mM), 22.1±6.7(0.3mM), 19.1±2.7(1mM)
	isaxonine	26.7±3.3(10mM)
	control	2.4±1.6
23	804	9.4±1.3(0.3mM), 13.0±2.1(0.5mM), 26.1±6.8(1mM), 18.8±3.1(2mM)
	isaxonine	28.5±5.4(10mM)
	control	1.4±0.2
24	1094	5.4±1.9(0.1mM), 16.9±1.2(0.3mM),

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
24	1094	10.9±1.1(1mM)
	1098	5.3±1.4(0.01mM), 10.2±0.9(0.03mM), 5.7±2.0(0.1mM)
	isaxonine	15.7±4.1(3mM)
	control	1.2±1.1
25	1162	4.7±3.0(0.03mM), 5.9±1.9(0.1mM)
	1102	11.9±0.7(0.1mM), 10.1±3.0(0.3mM)
	isaxonine	26.7±7.7(10mM)
	control	1.8±0.8
26	138	6.3±1.8(0.03mM), 12.6±4.1(0.1mM)
	2004	6.6±2.2(0.03mM), 30.2±6.4(0.1mM)
	171.3	28.8±3.1(0.1mM), 19.5±7.0(0.3mM)
	2052	4.6±2.1(0.01mM), 3.7±0.4(0.03mM)
	2060	3.6±0.1(0.03mM), 7.6±0.7(1mM)
	2070	5.6±3.9(0.1mM), 11.7±3.1(0.3mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
26	2076	4.8±1.4(0.01mM), 1.9±1.3(0.03mM)
	isaxonine	31.4±5.5(10mM)
	control	2.5±0.2
27	2084	11.1±2.2(0.03mM), 17.6±6.6(0.1mM)
	2092	23.9±0.4(0.1mM), 11.0±3.9(1mM)
	2100	4.4±0.8(0.03mM), 4.7±1.4(0.1mM)
	2108	4.8±2.0(0.03mM), 13.5±0.1(1mM)
	146	8.7±2.0(0.03mM), 40.0±6.1(0.1mM)
	147.1	6.6±0.4(0.03mM), 30.5±6.1(0.1mM)
	2116	34.2±3.8(0.1mM), 8.2±3.6(0.3mM)
	2124	12.5±5.3(0.03mM), 31.7±7.0(0.1mM)
	isaxonine	31.4±5.5(10mM)
	control	2.5±0.2
28	165	41.0±0.7(0.1mM), 12.4±1.8(0.3mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
28	166	36.8±7.1(0.1mM), 13.4±4.0(0.3mM)
	167	22.5±3.4(0.1mM), 9.3±2.3(0.3mM)
	169	34.1±5.7(0.1mM), 16.6±5.2(0.3mM)
	171	37.1±1.9(0.1mM), 8.8±2.6(0.3mM)
	171.1	36.4±7.8(0.1mM), 15.2±3.1(0.3mM)
	171.11	36.8±7.1(0.1mM), 14.3±3.0(0.3mM)
	isaxonine	21.0±2.3(10mM)
	control	2.5±0.2
29	2132	32.6±4.4(0.1mM), 31.7±5.0(0.3mM)
	2140	5.4±3.9(0.03mM), 17.0±1.2(0.1mM)
	2148	4.5±1.3(0.03mM), 4.2±1.2(0.1mM)
	2156	8.6±1.0(0.03mM), 19.6±5.3(0.1mM)
	307-1	3.6±0.4(0.03mM), 9.0±2.5(0.3mM)
	2164	4.6±1.1(0.1mM), 11.7±0.7(1mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
29	isaxonine	21.0±2.3(10mM)
	control	3.1±1.2
30	154	5.2±1.5(0.03mM), 16.2±2.1(0.1mM)
	2174	2.5±1.0(0.01mM)
	2182	8.0±3.2(0.03mM), 2.7±0.9(0.1mM)
	2188	2.4±0.9(0.1mM), 3.8±1.1(0.3mM)
	2194	9.5±3.5(0.1mM), 7.6±2.8(0.3mM)
	2202	2.2±2.0(0.1mM)
	2210	9.5±2.0(0.03mM), 9.5±1.9(0.1mM)
	isaxonine	19.4±2.4(10mM)
	control	1.7±0.9
31	2218	9.7±1.8(0.03mM), 11.4±6.1(0.1mM)
	662	3.1±1.6(0.1mM), 2.6±0.9(0.3mM)
	2226	6.4±3.3(0.03mM), 15.4±3.9(0.1mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
31	2234	5.1±3.2(0.03mM), 5.7±2.8(0.1mM)
	2242	3.3±0.9(0.03mM), 24.8±2.9(0.1mM)
	2250	10.9±3.9(0.1mM), 19.2±1.0(0.3mM)
	isaxonine	19.4±2.4(10mM)
	control	1.7±0.9
32	2260	2.2±0.3(0.03mM), 2.3±0.5(0.1mM)
	2270	14.7±5.1(0.03mM), 19.9±4.2(0.1mM) 21.3±3.5(0.3mM), 15.2±1.5(1mM)
	2278	13.9±6.3(0.03mM), 12.5±1.3(0.1mM)
	2286	9.7±5.4(0.03mM), 8.4±0.8(0.1mM)
	2294	3.7±0.9(0.03mM), 8.1±1.6(0.1mM)
	2302	8.0±2.7(0.03mM), 8.2±4.7(0.1mM)
	isaxonine	19.4±2.4(10mM)
	control	1.7±0.9
33	2012	6.6±1.2(0.03mM), 6.6±3.1(0.3mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
33	2020	4.6±1.1(0.03mM), 33.8±9.6(0.1mM), 30.5±9.5(0.3mM), 15.1±5.0(1mM)
	2028	4.0±0.8(0.03mM), 12.5±1.2(0.1mM)
	2036	3.9±0.8(0.03mM), 5.4±1.1(0.1mM)
	2044	3.7±0.7(0.01mM), 10.3±4.7(0.1mM)
	isaxonine	19.5±3.6(10mM)
	control	2.7±0.6
34	2310	8.3±1.8(0.1mM), 12.1±3.6(0.3mM)
	2318	7.7±1.4(0.03mM), 35.1±1.3(0.1mM), 18.6±5.2(0.3mM), 8.8±1.3(1mM)
	2326	4.6±1.4(0.03mM), 8.3±2.6(0.1mM)
	2334	13.2±0.2(0.03mM), 16.7±0.8(0.1mM)
	2342	5.9±2.1(0.03mM), 11.4±1.4(0.1mM)
	2350	5.9±1.5(0.3mM), 8.3±2.0(1mM)
	154.2	3.9±0.6(0.03mM), 8.9±2.4(0.1mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
34	171.5	7.2±1.1(0.01mM), 28.4±2.2(0.1mM), 32.7±0.6(0.3mM), 14.0±4.1(1mM)
	isaxonine	16.1±0.6(10mM)
	control	3.3±0.6
35	3104	2.8±0.8(0.03mM), 4.0±2.2(0.1mM), 7.2±2.8(0.3mM), 6.1±1.6(1mM)
	isaxonine	16.8±3.4(3mM)
	control	2.6±0.6
36	3144	20.8±4.7(0.03mM), 34.1±3.8(0.1mM), 44.5±9.7(0.3mM), 32.2±1.6(1mM)
	isaxonine	30.8±2.9(10mM)
	control	3.2±1.6
37	3200	3.6±0.5(0.03mM)
	isaxonine	23.3±2.9(10mM)
	control	2.3±0.6
38	3300	6.1±1.2(0.3mM), 7.8±1.0(1mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
38	3200	2.7±0.7(0.01mM), 2.5±2.3(0.03mM)
	isaxonine	19.4±3.1(3mM)
	control	3.2±1.2
39	3136	5.8±0.6(0.01mM), 13.8±4.8(0.03mM), 20.9±5.3(0.1mM), 7.1±3.0(0.3mM)
	isaxonine	22.6±0.5(10mM)
	control	1.8±1.4
40	3128	14.2±1.9(0.1mM), 11.9±4.5(0.3mM)
	3112	6.3±0.4(0.03mM), 6.2±3.4(0.1mM)
	3152	11.4±3.1(0.03mM), 6.8±4.2(0.1mM)
	3176	7.3±3.3(0.03mM), 23.1±4.8(0.1mM), 21.2±4.9(0.3mM), 14.6±5.0(1mM)
	3184	3.7±1.1(0.03mM), 13.9±2.3(0.1mM), 18.4±1.9(0.3mM), 17.0±2.1(1mM)
	3192	9.7±1.1(0.1mM), 3.7±3.2(0.3mM)
	isaxonine	19.4±3.1(10mM)

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
40	control	2.2±1.0
41	3404	3.3±1.3(0.03mM), 3.4±1.4(0.3mM)
	3412	2.9±0.9(0.03mM), 20.6±8.2(0.1mM)
	3420	4.2±1.9(0.03mM), 8.7±2.3(0.1mM)
	isaxonine	19.4±2.4(10mM)
	control	1.7±0.9
42	298	2.7±1.7(0.1mM), 6.1±5.6(0.3mM)
	306	7.7±0.5(0.03mM), 2.8±0.8(0.1mM)
	242	17.0±2.3(0.1mM), 12.8±6.3(0.3mM) 9.4±3.9(1mM)
	150	9.3±1.9(0.03mM), 13.6±1.2(0.1mM) 6.6±3.0(0.3mM)
	171-9	24.4±6.6(0.1mM), 7.1±2.9(0.3mM)
	isaxonine	12.1±1.6(3mM)
	control	2.4±0.4

- to be continued -

Table 12 (continued)

Run No.	Compound	Number of cells having neurites with a length at least two times the diameter of each cell/total number of cells, % (concentration of the compound)
43	171-11	5.9±0.9(0.03mM), 22.1±2.3(0.1mM) 29.2±1.5(0.3mM), 31.7±5.9(1mM)
	170-2	14.7±1.1(0.1mM), 5.6±2.1(0.3mM) 13.9±3.0(1mM)
	171-7	8.5±1.0(0.03mM), 6.7±3.1(0.1mM)
	171-12	13.3±1.1(0.1mM), 10.7±4.2(0.3mM) 12.7±0.9(1mM)
	isaxonine	14.9±1.9(10mM)
	control	2.5±1.0
44	2022-1	23.1±4.8(0.1mM), 18.1±2.8(0.3mM) 19.8±2.1(1mM)
	2023-1	8.3±2.1(0.1mM), 7.0±0.5(0.3mM)
	isaxonine	20.1±3.0(10mM)
	control	3.2±0.9

Table 13

Activity on NS-20Y cells

Compound	Number of cells in which neurites appeared/total number of cells (concentration of the compound)	
	24 hours	48 hours
112	4/51(0.025mM)	9/50(0.025mM) 4/49(0.01mM)
control	0/51	1/51
120	23/50(0.5mM)	4/50(0.5mM)
control	1/49	0/50
144	37/50(0.1mM)	31/50(0.1mM) 8/52(0.05mM)
control	0/50	1/50 6/50(0.025mM)
152	3/50(0.05mM)	2/50(0.025mM)
control	0/50	0/50
160	10/53(0.5mM)	2/50(0.5mM)
control	0/50	0/50
168	26/50(0.1mM) 12/50(0.25mM)	20/55(0.1mM)
control	3/50	2/50
208	27/53(0.1mM) 17/51(0.25mM)	28/50(0.1mM)
control	1/50	0/52

- to be continued -

Table 13 (continued)

Compound	Number of cells in which neurites appeared/total number of cells (concentration of the compound)	
	24 hours	48 hours
128	23/55(1.0mM) 4/49(0.3mM)	31/50(0.3mM) 21/50(0.5mM)
control	3/50	4/50
216	3/49(0.025mM)	24/50(0.025mM) 20/50(0.05mM)
control	0/51	1/50
232	2/50(0.025mM)	2/49(0.01mM)
control	0/51	0/50
240	4/50(0.2mM)	3/50(0.2mM)
control	0/50	0/50
248	3/49(0.1mM)	2/50(0.05mM)
control	0/49	0/50
256	5/51(0.2mM)	2/48(0.05mM)
control	0/51	0/50
272	33/50(0.1mM) 24/50(0.2mM)	17/50(0.1mM)
control	0/50	0/51
280	3/50(0.2mM)	8/53(0.1mM)
control	0/50	1/53

- to be continued -

Table 13 (continued)

Compound	Number of cells in which neurites appeared/total number of cells (concentration of the compound)	
	24 hours	48 hours
288	2/52(0.1mM)	2/50(0.1mM)
control	0/50	0/50
296	9/49(0.1mM)	2/50(0.1mM)
control	0/50	0/48
304	40/50(0.1mM)	3/50(0.01mM)
control	0/50	0/51
328	32/50(0.1mM)	8/50(0.025mM) 12/51(0.1mM)
control	0/51	0/50
336	3/54(0.2mM)	2/50(0.5mM)
control	0/52	0/50
344	3/51(0.2mM)	2/49(0.5mM)
control	0/50	0/51
368	14/50(0.1mM)	8/51(0.05mM) 5/50(0.1mM)
control	0/50	0/50
376	2/50(0.2mM)	2/50(0.1mM)
control	0/50	0/50

- to be continued -

Table 13 (continued)

Compound	Number of cells in which neurites appeared/total number of cells (concentration of the compound)	
	24 hours	48 hours
392	8/50(0.1mM)	6/51(0.05mM) 3/43(0.1mM)
control	0/52	0/50
612	2/50(0.1mM)	2/50(0.1mM)
control	0/50	1/51
668	2/50(0.1mM)	2/50(0.05mM)
control	0/50	0/50
684	2.50(0.1mM)	2/50(0.05mM)
control	0/53	0/50
1094	7/48(0.4mM) 4/54(0.1mM)	2/50(0. mM)
control	2/50	1/50
1026	31/50(0.1mM) 4/50(0.02mM)	2/50(0.02mM)
control	2/50	1/50
1086	4/50(0.4mM)	2/50(0.02mM)
control	2/50	1/50
1090	21/50(0.1mM) 4/50(0.02mM)	3/50(0.1mM)
control	1/50	1/50

- to be continued -

Table 13 (continued)

Compound	Number of cells in which neurites appeared/total number of cells (concentration of the compound)	
	24 hours	48 hours
1014	9/50(0.4mM) 3/50(0.1mM)	6/50(0.4mM)
control	2/50	2/50
384	8/50(0.4mM)	3/50(0.4mM)
control	2/50	1/50
416	11/50(0.4mM) 7/50(0.1mM)	2/50(0.1mM)
control	1/50	0/50
320	8/50(0.1mM)	6/50(0.1mM)
control	2/50	1/50
400	30/53(0.4mM) 9/50(0.1mM)	3/48(0.4mM) 3/50(0.1mM)
control	2/50	1/50
136	42/50(0.4mM) 9/50(0.1mM)	15/50(0.4mM)
control	3/50	1/50
264	8/48(0.4mM)	4/50(0.4mM)
control	2/50	1/50
424	16/50(0.4mM)	3/50(0.4mM)
control	3/52	1/50

- to be continued -

Table 13 (continued)

Compound	Number of cells in which neurites appeared/total number of cells (concentration of the compound)	
	24 hours	48 hours
360	18/50(0.1mM) 8/50(0.02mM)	4/50(0.1mM)
control	3/50	1/50
224	6/50(0.02mM)	3/50(0.02mM)
control	1/50	1/50
432	7/50(0.4mM) 7/50(0.02mM)	4/50(0.4mM)
control	2/50	2/50
200	4/50(0.02mM)	2/50(0.02mM)
control	2/50	1/50
192	23/50(0.4mM)	4/50(0.4mM)
control	2/50	1/50
176	8/50(0.1mM)	2/50(0.02mM)
control	1/50	0/50
184	8/50(0.02mM) 5/48(0.1mM)	3/50(0.02mM)
control	1/52	1/50
628	9/50(0.1mM)	3/50(0.1mM)
control	3/50	1/50

- to be continued -

Table 13 (continued)

Compound	Number of cells in which neurites appeared/total number of cells (concentration of the compound)	
	24 hours	48 hours
700	6/50(0.4mM) 4/53(0.1mM)	4/50(0.1mM)
control	2/50	1/50
660	5/50(0.1mM)	4/50(0.1mM)
control	2/50	1/50
604	7/50(0.4mM) 6/50(0.02mM)	2/50(0.02mM)
control	2/50	1/50
804	8/55(0.25mM) 7/50(0.5mM)	25/51(0.5mM) 8/50(0.25mM)
control	4/50	0/50
168	26/50(0.1mM) 12/50(0.25mM)	20/55(0.1mM)
control	3/50	2/50
208	27/53(0.1mM) 17/51(0.25mM)	28/50(0.1mM)
control	1/50	0/52
820	5/53(0.5mM) 4/50(0.1mM)	5/55(0.25mM) 4/50(0.1mM)
control	3/50	0/50

- to be continued -

Table 13 (continued)

Compound	Number of cells in which neurites appeared/total number of cells (concentration of the compound)	
	24 hours	48 hours
828	10/58(0.3mM) 5/59(0.5mM)	6/50(0.3mM) 5/51(0.5mM)
control	2/50	2/51
812	11/50(1.0mM) 9/50(0.5mM)	9/50(0.3mM) 5/51(0.5mM)
control	2/53	2/50
3192	6/50(0.02mM)	4/50(0.02mM)
control	1/50	0/50
242	6/50(0.4mM) 4/50(0.2mM)	11/50(0.2mM) 6/50(0.1mM)
control	0/50	0/50
2022-1	12/50(0.2mM) 5/50(0.4mM)	2/50(0.1mM)
control	0/50	0/50
2023-1	2/50(0.1mM)	2/50(0.2mM)
control	0/50	0/50
171-9	7/45(0.4mM)	2/50(0.02mM)
control	0/50	0/50
171-11	5/50(0.3mM)	2/50(0.1mM)

- to be continued -

Table 13 (continued)

Compound	Number of cells in which neurites appeared/total number of cells (concentration of the compound)	
	24 hours	48 hours
control	0/50	9/50
170-2	3/50(0.1mM)	2/50(0.1mM)
control	0/50	0/50
171-7	4/50(0.1mM)	2/50(0.1mM)
control	0/50	0/50

EXPERIMENTAL EXAMPLE 2

Therapeutic effect on rats with crushed sciatic nerves:-

The therapeutic effect of the compound of the invention was tested on rats having crushed sciatic nerves as a model of peripheral nervous disorder using (1) a change in the action of the hind paw with the crushed sciatic nerves and (2) a change in the weight of the muscle as an index of the course of degeneration and regeneration of peripheral nerves.

In the experiment, male Wistar rats (6 weeks old), seven per group, were used. The sciatic nerves were crushed by a method similar to the method of Yamatsu et al. (see Kiyomi Yamatsu, Takenori Kaneko, Akifumi Kitahara and Isao Ohkawa, Journal of Japanese Pharmacological Society, 72, 259-268 (1976) and the method of Hasegawa et al. (see Kazuo Hasegawa, Naoji Mikuni and Yutaka Sakai, Journal of Japanese Pharmacological Society, 74, 721-734 (1978). Specifically, under anesthesia with pentobarbital (40 mg/kg, i.p.), the left side sciatic nerve was exposed at the femur, and a specific site of the exposed sciatic nerve was crushed for 30 seconds by using a hemostat. After the crushing, the opetation site was immediately sutured. Thereafter, vincristine known to retard the regeneration of the peripheral nerve was intraperitoneally administered in a dose of 100 g/kg once a week.

Compounds of the invention were selected as test drugs, and administered intraperitoneally once a day from the day of crushing to 30th day from then. To a control group, only 0.9 % saline was administered.

(1) Functional change in the hind paw with crushed nerves

Twitch tension, which is a transient tension incident to contraction of the dominated muscles that occurs by electrical stimulation or the like of motor nerves, as is the case with the interdigit distance to be described, is considered to reflect functional changes of the nerves and muscles.

Thus, 30 days later, under aesthesia with chloral hydrate (400 mg/kg, i.p.), the twitch tension of rats was

measured by the method of Kern et al. [J. Neurosci. Methods, 19, 259 (1987)]. Specifically, the hair on the hind paw of rats was shaven, and coated with Cardiocream (a product of Nihon Denko K.K.). Then, to the skin of the hind paw, electrodes with an alligator were attached. The cathode was attached to the rear portion of the trochiter, and the anode, to a site 1 cm rearwardly of the anode electrode and 1 cm toward its back. The rat was fixed on its back, and the hind paw to be measured was fixed perpendicularly. A silk yarn, about 20 cm long, was connected at one end to the third efferent toe joint of the hind paw to be measured and at the other end to a tension transducer. Isotonic contractions of the third muscle digitus flexus were recorded on a polygraph. Electrical stimulation was effected at a voltage of 100 V for a continuous duration of 1 msec. with rectangular waves at a frequency of 2 Hz. The static tension was 15 to 30 g, and 10 stimulations were repeated 3 times with intervals of 15 seconds. The contracting force was expressed as tension (g). From the measured values of both paws, the recovery ratio (%, left/right) of the contracting force of the paw with crushed nerves was calculated. The results are shown in Tables 14 and 15.

Table 14

Twitch tension			
Compound	Dose (mg/kg)	Number of cases	Twitch tension*1 left/right (%)
Saline	-	7	33.3 ± 7.0
168	10	7	48.4 ± 11.8*2
168	30	8	51.2 ± 13.6*3
296	30	8	48.1 ± 9.4*2

*1 mean ± S.D.,
*2 $p<0.05$,
*3 $p<0.01$

Table 15

Twitch tension				
Compound	Dose (mg/kg)	Number of cases	Twitch tension left/right (%)	
			18th days	23rd days
Physiological saline	-	7	44.2±17.6	49.8±14.8
3144	30	8	54.5±17.1	57.9±15.5

The test compounds evidently increased the recovery of twitch tension, which is an electrophysiological index, and improved symptom, over the control group.

The distance between digits was measured because this is a good index which functionally shows the degeneration and regeneration of the nerve and its change can be measured with the lapse of time.

By a method similar to the method of Hasegawa [Hasegawa, K., Experientia, 34, 750-751 (1978)], the distance between the first and fifth digits of the hind paw was measured.

The ratio of the measured distance to the interdigit distance in a normal hind paw was calculated and expressed in percentage (%). The interdigit distance of the hind paw with crushed nerves was less than 50 % of that in a normal hind paw immediately after the crushing. Recovery of the interdigit distance began 12 to 16 days later, and in drug-administered groups, there was evidently a tendency to accelerated recovery in comparison with the control group from about 17th day to the final day (26th).

One example is shown in Table 16.

Table 16

Therapeutic effect on rats having crushed sciatic nerves			
Compound	Dose (mg/kg, i.p.)	Recovery of the interdigit distance	
		18th days	23rd days
Physiological saline	1 ml/kg	67.6±16.1	76.5±20.2
3144	30	72.7±14.0	83.8±12.2

(2) Change in the weight of muscle

It is known that removal of a nerve or its disorder causes atrophy of the muscle which is under its control, and the atrophy is gradually cured by re-control by the nerve. For this reason, a change in the weight of the muscle, which is quantitative, was selected as an index. Thirty days after the operation, the muscles extensor digitorum longus of both hind paws which are muscles under the control of sciatic nerves were extracted under anesthesia, and their weights were measured. The ratio of the weight of the muscle extensor digitorum longus on the crushed side to that of normal side was calculated and expressed in percentage (%). The results are shown in Table 17.

Table 17

Compound	Dose (mg/kg)	Number of cases	Weight of muscle extensor digitorum longus *1 left/right (%)
Saline	-	7	48.8 ± 6.4
168	10	7	52.1 ± 5.4
168	30	8	59.4 ± 11.8*2
296	30	8	56.9 ± 9.7*2

*1 mean ± S.D.,
*2 $p<0.05$

The results show that the test compounds, in comparison with the control, evidently increased the weight % of muscle extensor digitorum longus.

Accordingly, these test compounds are useful as improvers and therapeutic agents for peripheral nerve disorders.

EXPERIMENTAL EXAMPLE 3

Promoting effect on the improvement of motor imbalance due to injury of the rat's brain cells by transplantation of fetal cerebral cells:-

Nigral dopaminergic nerve cells at the left side of the brain of 4-week old female Wistar rats (body weight 100 g) were lesioned by injecting a very small quantity of 6-hydroxydopamine. The rats showed a tendency to rotate spontaneously in a direction opposite to the lesioned side for several days, but no apparent abnormal action was observed after that. Upon administration of methamphethamine (5 mg/kg, i.p.) to the rats having the lesioned nigral dopaminergic nerve cells, they began rotational movement toward the

lesioned side.

After two weeks from the destruction by the administration of the drug, portions of the truncus corporis callosi containing dopamine cells (i. e., substantia nigra and the tagmentum at the abdomen side) were cut from the brain of a fetal rat of 14 to 17 days of age, cut finely, and treated with trypsin. Then, the extracted tissues were incubated at 37° C for 30 minutes, and the tissues were subjected to pipetting to form a suspension. Five microliters of the suspension was transplanted each into two sites of the caudate nucleus of the lesioned side (10 microliters in total, about 10^5 cells).

Compound No. 168 of the invention was administered in a dose of 156 mg/kg (i.p.) for 4 days from the day of transplantation, then with a suspension of 7 days, for 10 days in a dose of 50 mg/kg (i.p.) from the 11th day. Compound No. 296 was administered in a dose of 153 mg/kg, and then 50 mg/kg, in accordance with the same schedule.

Compound No. 3144 was also administered in accordance with the same schedule in a dose of 135 mg/kg, and then 45 mg/kg.

The rotational movements induced by administra tion of methamphetamine were examined 2 weeks and 1 week before, and 2 (or 3), 4, 6 and 8 weeks after, the transplantation and the administration of the drug. The number of rotational movements for the first one minute was counted at intervals of 10 minutes after the administration of methamphetamine, and the total number of rotational movements counted six times was averaged to find a mean number of the rotational movements.

The results are shown in Table 18.

The results show that the test compounds are useful as improvers and therapeutic agents for cental nerve disorders.

Table 18

Compound	-1 W	3 W	4 W	6 W	8 W
168	13.3±7.8	9.1±5.6	4.5±4.5	1.5±3.9	0.8±2.1
296	13.2±4.1	8.4±5.0	3.1±3.4	0.9±2.3	1.0±1.5
3144	14.1±4.7	7.7±4.7	4.0±5.6	0.2±2.2	1.1±4.1
Physiological saline	16.7±9.1	11.2±9.6	5.3±8.3	2.8±5.4	2.2±6.0

EXPERIMENTAL EXAMPLE 4

Improvement of learning and memory of mice with nerve disorder induced by mercury poisoning, and recovery effect:-

Male BalbC strain mice, 7 weeks old, were first caused to learn a T-shaped maze three times in a week so that they run straight from a starting point to a safety area. Then, methylmercury chloride (MMC for short) was administered orally in a dose of 6 mg/kg/day for 6 days to male Balb C strain mice (7 weeks old). A group of mice to which saline was administered in a dose of 0.1 ml/10 g/day was used as a control group. Beginning with the day next to the day of administering MMC, compounds of the invention were intraperitoneally administered over 10 days. On the sixth day after administration of the drug (namely, on the 12th day after start of the experiment), learning of the T-shaped maze was resumed, and the running behaviors of the mice were observed. The number of mice which could be experimented in the T-shaped maze on the 10th and 11th days after the resumption (21st and 22nd days after the start of the experiment) was counted and expressed as a denominator. The number of mice which ran to the safety area within 5 seconds at least 8 times out of ten trial runnings was counted and expressed as a numerator. The decrease in the number of the test animals was due to death by MMC poisoning. The time (seconds) required for the animals to run to the safety area was measured, and the mean ± standard error (SE) was calculated.

The results demonstrate the effect of the compounds of the invention to improve learning and momory of the mice and their recovery effect.

EXPERIMENTAL EXAMPLE 5

The acute toxicity of the compounds of the invention was examined by the following method.

Male ddy-strain 5-week old mice, 4-6 per group, were used as experimental animals. Each of the compounds was intraperitoneally (i.p.), and the toxicity of the compound was assessed 24 hours after the administration. The results are shown in Table 19.

Table 19

Acute toxicity on mice

Compound	Estimated LD_{50} (mg/kg, i.p.)
128	>1000
136	>1000
144	>1000
152	>1000
168	>1000
208	>1000
392	500-1000
328	>1000
408	500-1000
240	>1000
296	>1000
272	>1000
170	>1000
604	<500
644	>1000
304	>1000
360	>1000
376	500-1000
424	>1000
248	>1000
216	>1000
1090	500-1000
1158	<250
612	500-1000
184	>1000
192	500-1000
280	500-1000
232	>1000
112	>1000

- to be continued -

Table 19 (continued)

Compound	Estimated LD_{50} (mg/kg, i.p.)
120	>1000
160	>1000
176	>1000
264	500-1000
312	>1000
320	>1000
352	500-1000
368	500-1000
400	500-1000
628	500-1000
660	500-1000
684	500-1000
804	500-1000
104	500-1000
138	>1000
2004	>1000
146	>1000
154	>1000
147.1	>1000
169	>1000
2116	500-1000
2124	>1000
171.3	>1000
256	>1000
288	500-1000
2132	>1000
2140	>1000
2020	500-1000
2028	500-1000
2044	500-1000

- to be continued -

Table 19 (continued)

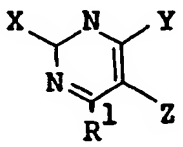
Compound	Estimated LD_{50} (mg/kg, i.p.)
2070	>1000
2084	>1000
2092	>1000
2156	>1000
2164	>1000
2182	500-1000
2210	500-1000
2218	500-1000
2242	500-1000
2250	500-1000
2270	>1000
2278	500-1000
2302	500-1000
2318	500-1000
2326	500-1000
2342	500-1000
154.2	500-1000
171.5	>1000
2310	500-1000
2350	500-1000
3104	>1000
3122, 3144, 3176, 3184, 3192, 3412 and 3420	500-1000
2318	>1000
2334	>1000
171-9	500-1000
171-11	>1000
170-2	500-1000
170-12	>1000
2022-1	>1000

The compounds of general formulae (1), (2) and (3) provided by this invention have a promoting effect on the proliferation of nerve cells and the formation and sprouting of neurites and a nerve regenerating effect and a motor function recovering effect in rats and mice having nerve disorders, and can be used suitably for improving and curing neurological diseases such as disorders of peripheral nerves or central nerves and dementia. They are expected to be used also suitably for the recovery, improving and curing of neurological diseases caused by nervous tissues and cells which have to do with perceptive and sensory functions and an autonomic function.

It has been found that the compounds of the invention have biological activities equal to, or higher than, those of isaxonine and mecobalamin as a control as shown in Experimental Examples 1 to 4 and Tables 12 to 19. The toxicity of the compounds of this invention are generally weak as shown in Experimental Example 5. Thus, the compounds of this invention are generally considered to be highly active and highly safe drugs and very useful with weak toxicity.

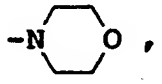
Claims

1. A pyrimidine represented by the following formula (1), or its pharmaceutically acceptable salt,

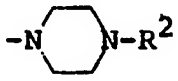


(1)

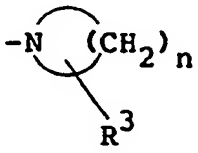
wherein R^1 represents a hydrogen atom or a lower alkyl group; X represents a group of the formula



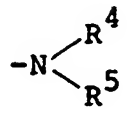
a group of the formula



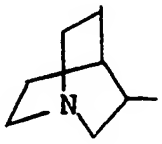
in which R^2 represents a hydrogen atom, a lower alkyl group, a phenyl group, a benzyl group or an alpha-(p-chlorophenyl)benzyl group,
a group of the formula



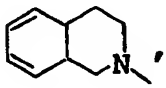
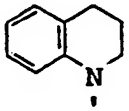
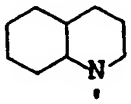
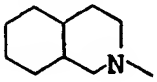
in which R^3 corresponds to one or at least two identical or different substituents replacing one or at least two hydrogen atoms of identical or different methylene groups, and represents a lower alkyl group, a hydroxyl group, a phenyl group optionally substituted by nitro, a benzyl group, a benzoyloxy group, a benzoylamino group, a lower alkylamino group, a di-lower alkylamino group, the $HO(C_6H_5)_2C$- group, a piperidino group, a hydroxy(lower alkyl) group, the $C_6H_5SO_2O$- group, a benzoyl group optionally substituted by halogen, a lower alkylsulfonylamide group or a lower alkoxycarbonyl group, and n is a number of 4, 5, 6 or 7,
a group of the formula



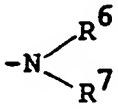
in which R^4 represents a hydrogen atom, a lower alkyl group or a benzyl group, and R^5 represents a lower alkyl group, a lower acyl group, a 2-furoyl group, a benzyl group, a 4-piperidyl group optionally substituted by benzoyl, a phenethyl group, the group



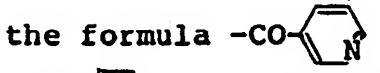
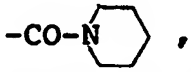
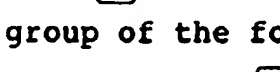
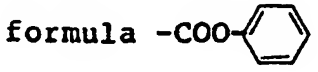
or a benzoyl group optionally substituted by halogen or nitro,

a group of the formula  , a group of the formula  , a group of the formula  , or a group of the formula  ;

Y represents a group of the formula $-CH_2R^3$
wherein R^3 represents a hydrogen atom, a lower alkyl group, a lower alkoxy group, a lower alkylthio group, or a di-lower alkylamino group,
a group of the formula

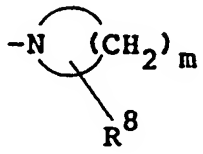


wherein R^6 represents a hydrogen atom, a lower alkyl group, a phenyl group, a benzyl group, a lower alkoxy group or a 2-(N,N-dimethylamino)ethyl group, and R^7 represents a lower alkyl group, a lower acyl group, a cyclohexylcarbonyl group, a 2-furoyl group, a lower alkoxycarbonyl group, a cinnamoyl group, a benzyl group, a benzylcarbonyl group, a tosyl group, a phenoxyacetyl group, a di-lower alkylcarbamoyl group, a 2-thienyl group,

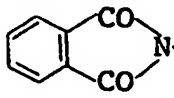
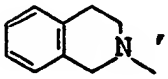
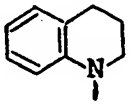
a group of the formula  , a group of the formula  , a group of the formula  , a group of the formula  , a group of the formula  ,

a 4-lower alkylpiperazyl group, or a benzoyl group optionally substituted by halogen, nitro, lower alkyl, lower

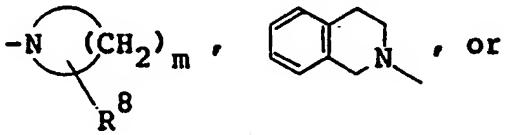
alkoxy, amino, benzoylamino or phenyl, provided that when R^6 is a hydrogen atom, R^7 is a benzoyl group, a group of the formula

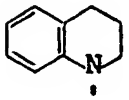


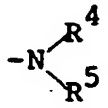
wherein R^8 corresponds to a substituent replacing the hydrogen atom of the methylene group, and represents a hydrogen atom, a lower alkyl group, a phenyl group or a benzyl group, and m is a number of 4, 5, 6 or 7,

a group of the formula  , a group of the formula  , or a group of the formula  ;

and Z represents a hydrogen atom, a halogen atom, a lower alkyl group or a lower alkoxycarbonyl group; provided that Y represents $-CH_2R^9$ only when Z is a lower alkoxycarbonyl group; that R^4 represents a hydrogen atom only when R^5 represents a lower alkyl group, a lower acyl group, a 2-furoyl group, a benzyl group, a phenethyl group or a benzoyl group optionally substituted by halogen or nitro, Y represents CH_2R^9 and Z represents a lower alkoxy carbonyl group; that Y can be



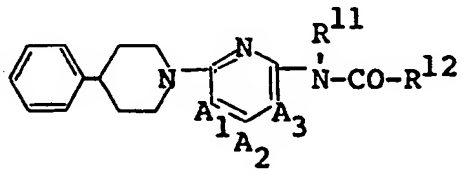


only when X is 

and R^4 is a lower alkyl group.

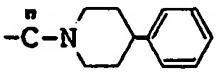
2. The compound of claim 1 in which the pharmaceutically acceptable salt is selected from the group consisting of hydrochlorides, hydrobromides, bisulfites, phosphates, acidic phosphates, acetates, maleates, fumarates, succinates, lactates, tartrates, benzoates, citrates, glucanates, methanesulfonates, p-toluenesulfonates, naphthalenesulfonates and quaternary ammonium salts.

3. A compound represented by the following formula (2), or its pharmaceutically acceptable salt,

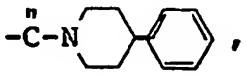


(2)

wherein A_1 represents =CH- or -N=; A_2 is =CH-, -N=, or

 ;

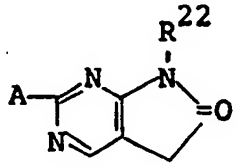
A_3 represents =CH- or -N=; R^{11} represents a lower alkyl group; R^{12} represents a phenyl group optionally substituted by halogen, lower alkyl or lower alkoxy, a 2-furyl group, or a 2-thienyl group; provided that when A_1 is -N=, A_2 is



when A_1 and A_2 are =CH-, A_3 is =CH-, and
when A_2 is -N=, A_1 and A_3 are =CH-.

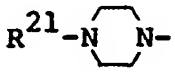
4. The compond of claim 3 in which the pharmaceutically acceptable salt is selected from the group consisting of hydrochlorides, hydrobromides, bisulfites, phosphates, acidic phosphates, acetates, maleates, fumarates, succinates, lactates, tartrates, benzoates, citrates, glucanates, methanesulfonates, p-toluenesulfonates, naphthalenesulfonates and quaternary ammonium salts.

5. A compound of the following formula (3), or its pharmaceutically acceptable salt,

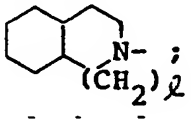


(3)

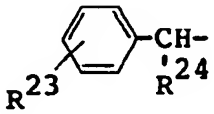
wherein A represents a group of the formula



or a group of the formula

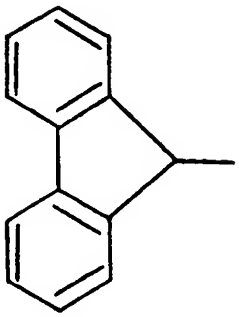


R^{21} represents a group of the formula (a)



(a)

wherein R^{23} represents a hydrogen atom, a lower alkyl group, a lower alkoxy group or a phenyl group and R^{24} represents a hydrogen atom, a lower alkyl group, a cyclohexyl group, a phenyl group, a 4-halogenophenyl group, a p-diphenyl group, a 2-pyridyl group or a 2-thiophenyl group, provided that R^{23} and R^{24} are not hydrogen atoms at the same time;
or a group of the formula (b)



which is a 9-fluorenyl group or a triphenylmethyl group; R^{22} represents a lower alkyl group; and l is a number of 0 or 1.

6. The compound of claim 5 in which the pharmaceutically acceptable salt is selected from the group consisting of hydrochlorides, hydrobromides, bisulfites, phosphates, acidic phosphates, acetates, maleates, fumarates, succinates, lactates, tartrates, benzoates, citrates, glucanates, methanesulfonates, p-toluenesulfonates, naphthalenesulfonates and quaternary ammonium salts.

7. A therapeutical composition for use in the treatment of neurological diseases comprising a compound or pharmaceutically acceptable salt as claimed in any one of the preceding claims as an active ingredient.

8. Use of a compound or pharmaceutically acceptable salt as claimed in any one of claims 1 to 6, in the preparation of a pharmaceutical composition containing said compound or salt as active ingredient for use in the treatment of neurological diseases.

9. A compound or pharmaceutically acceptable salt as claimed in any one of claims 1 to 6 for use in the treatment of neurological diseases.